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A 45-year-old woman comes to the office due to polyuria and nocturia. She has no fever, dysuria, or abdominal pain. The patient has no significant medical problems and takes no medications. Her temperature is 36.7 C (98 F), blood pressure is 120/80 mm Hg, and pulse is 76/min. The patient's mucous membranes appear dry. The remainder of her physical examination is normal. Her urine output and osmolality remain unchanged with water deprivation for several hours, but after administration of desmopressin, urine output decreases and urine osmolality increases. Renal clearance of which of the following substances would decrease the most after this patient's injection?

A. Calcium

B. Creatinine

C. Glucose

D. Para-amino hippuric acid

E. Urea

Submit

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31

A 45-year-old woman comes to the office due to polyuria and nocturia. She has no fever, dysuria, or abdominal pain. The patient has no significant medical problems and takes no medications. Her temperature is 36.7 C (98 F), blood pressure is 120/80 mm Hg, and pulse is 76/min. The patient's mucous membranes appear dry. The remainder of her physical examination is normal. Her urine output and osmolality remain unchanged with water deprivation for several hours, but after administration of desmopressin, urine output decreases and urine osmolality increases. Renal clearance of which of the following substances would decrease the most after this patient's injection?

A. Calcium (13%)
B. Creatinine (9%)
C. Glucose (10%)
D. Para-amino hippuric acid (13%)
✓ E. Urea (53%)

Omitted
Correct answer
E

53%
Answered correctly

04 mins, 30 secs
Time Spent

04/20/2020
Last Updated

Explanation

Renal handling of urea in the setting of high ADH

Portion of the nephron impermeable to urea

Urea

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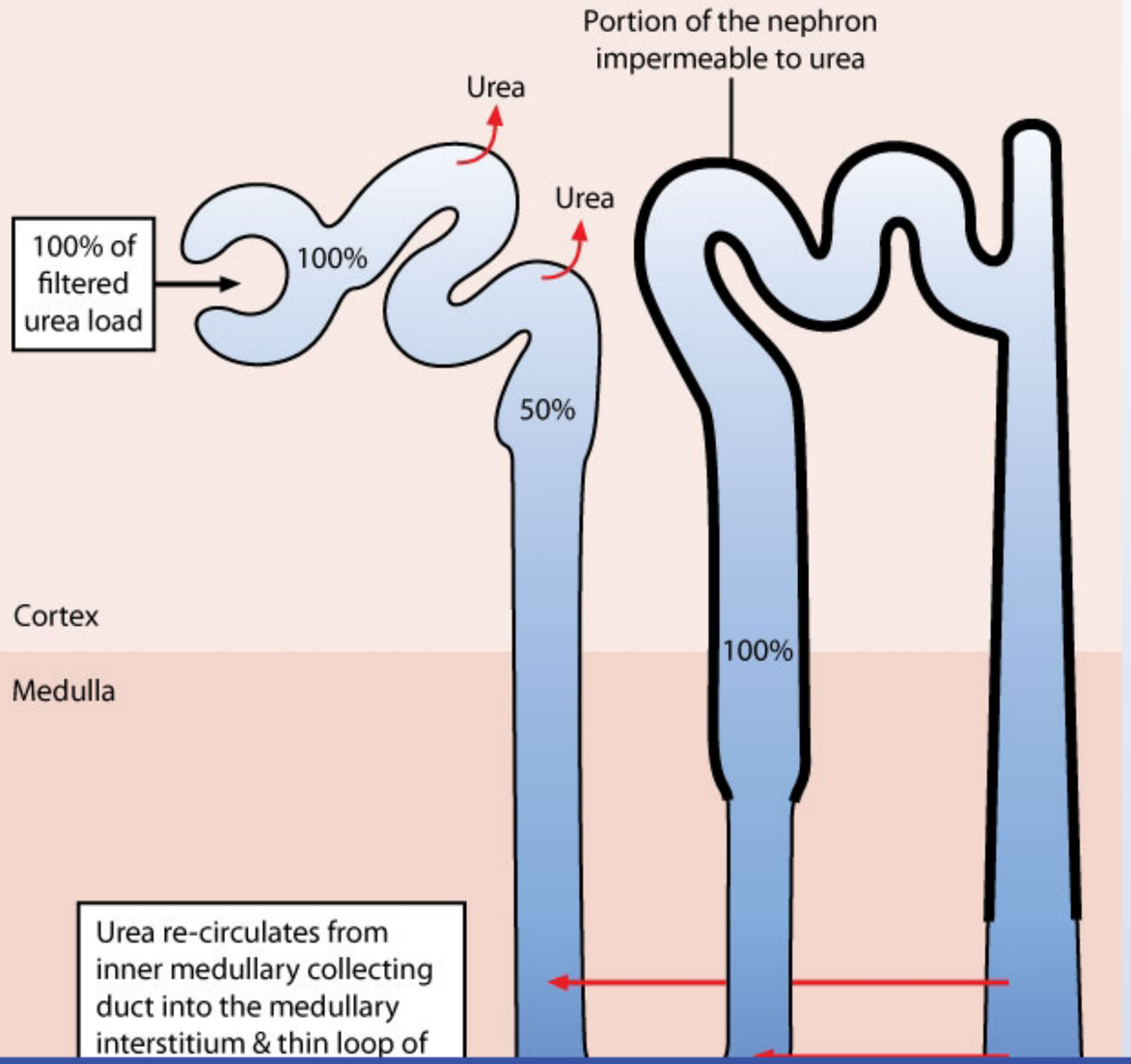
Renal handling of urea in the setting of high ADH



Explanation

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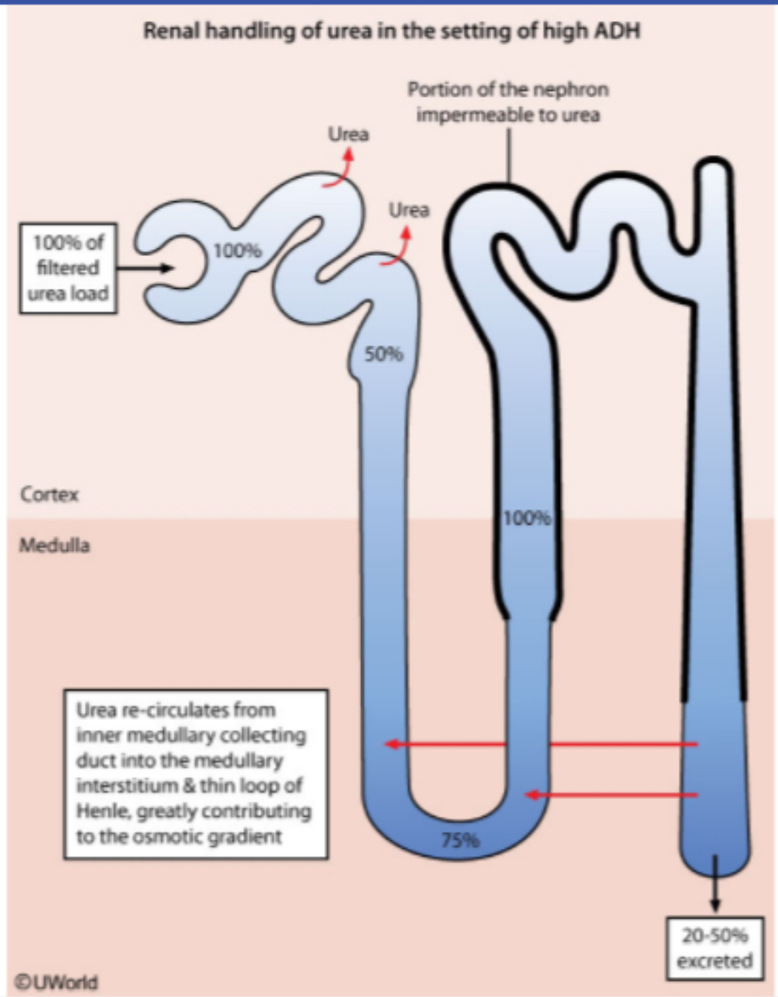

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inner medullary collecting

Polyuria that resolves with the administration of desmopressin (DDAVP, synthetic analogue of vasopressin) is likely secondary to deficient vasopressin secretion (central diabetes insipidus). **Vasopressin** produces a V_2 receptor-mediated increase in water permeability within the cortical and medullary collecting ducts. As water leaves the tubular fluid, urea concentration greatly increases in these tubular segments. Although the cortical collecting duct is impermeable to urea, vasopressin activates urea transporters in the **medullary collecting duct**, increasing urea reabsorption and **decreasing renal urea clearance**. This passive reabsorption of urea into the medullary interstitium in the presence of ADH significantly increases the medullary osmotic gradient, allowing the production of maximally concentrated urine.

(Choice A) The majority of filtered calcium is passively absorbed in the proximal tubule and ascending limb of Henle's loop. Further calcium reabsorption by the distal and collecting ducts is stimulated by parathyroid hormone (not vasopressin).

(Choice B) Creatinine is freely filtered by the glomerulus, and a small amount is also secreted by the proximal tubule. No further secretion or reabsorption occurs beyond the proximal tubule.

(Choice C) Glucose is filtered in the glomerulus and fully reabsorbed in the proximal tubule as long as the filtered glucose is lower than the transport maximum (Tm). Sodium-glucose cotransporter-2 (SGLT-2) receptor inhibitors act on the tubular receptors to lower the Tm of glucose and may be used as third-line agents in type 2 diabetes mellitus.

(Choice D) Para-amino hippuric (PAH) acid is filtered in the glomerulus and nearly completely secreted by the proximal tubules without significant tubular reabsorption. PAH clearance depends on renal plasma flow. Unlike vasopressin, desmopressin selectively activates V_2 receptors and does not cause vasoconstriction (mediated by V_1 receptors).

Educational objective:
Vasopressin and desmopressin cause a V_2 receptor-mediated increase in water and urea permeability at the inner medullary collecting duct. The resulting rise in urea reabsorption (decreased urea clearance) enhances the medullary osmotic gradient, allowing the production of maximally concentrated urine.

Physiology	Renal, Urinary Systems & Electrolytes	Diabetes insipidus
Subject	System	Topic

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A 56-year-old woman with polycystic kidney disease comes to the office for follow up. Her renal function has been gradually declining, and she is being considered for hemodialysis in the near future. The patient has recently experienced increasing exertional dyspnea and fatigue but has had no fever, dysuria, or flank pain. Other medical conditions include hypertension and renal calculi. Blood pressure is 130/86 mm Hg and pulse is 80/min. Physical examination shows mucosal pallor. The lungs are clear on auscultation and heart sounds are normal. Abdominal examination reveals palpably enlarged kidneys. There is no lower extremity edema. Laboratory results show normocytic, normochromic anemia, which is attributed to insufficient hormone production by the kidneys. This hormone is predominantly secreted by which of the following parts of the kidney?

A. Efferent arteriolar smooth muscles
B. Glomerular podocytes
C. Juxtaglomerular cells
D. Peritubular interstitial cells
E. Proximal tubule epithelium

Submit

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A. Efferent arteriolar smooth muscles (3%)
B. Glomerular podocytes (0%)
C. Juxtaglomerular cells (17%)
✓ D. Peritubular interstitial cells (66%)
E. Proximal tubule epithelium (11%)

Omitted
Correct answer
D

66%
Answered correctly

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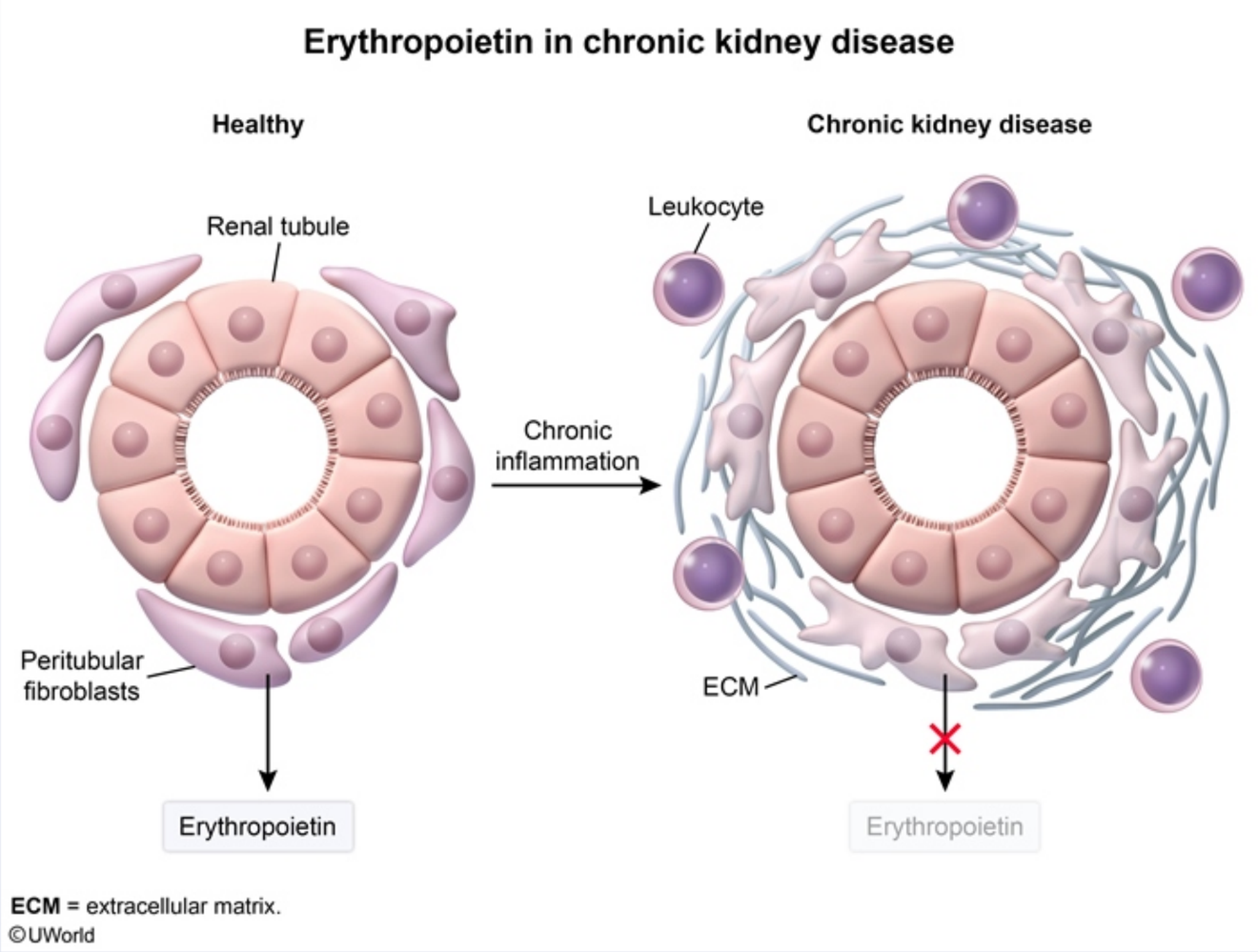
Time Spent

03/22/2020
Last Updated

Explanation

Erythropoietin in chronic kidney disease

Healthy | Chronic kidney disease



Patients with **chronic kidney disease** (CKD) often develop symptomatic anemia (eg, fatigue, exertional dyspnea) as the glomerular filtration rate declines. Most cases are due to the **inadequate secretion of erythropoietin** (EPO), a glycoprotein hormone produced by **peritubular fibroblasts in the renal cortex** in response to tissue hypoxia (as is seen with anemia). EPO acts on erythrocyte precursor cells (erythroid colony–forming unit cells) in the bone marrow to stimulate red blood cell differentiation and survival.

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Healthy patients increase EPO levels up to 10,000-fold in response to anemia, but patients with CKD have chronic inflammatory damage to renal EPO-producing cells and are often unable to generate sufficient EPO to maintain red blood cell counts. These individuals are often treated with **synthetic EPO agents** (eg, epoetin, darbepoetin) to stimulate erythrocyte production. As iron is rapidly consumed to make red blood cells, individuals treated with EPO agents are often also given iron supplementation to prevent the development of iron deficiency anemia.

In adults, approximately 80% of EPO is generated in the kidney; the remainder is largely generated in the liver by hepatocytes and Ito perisinusoidal cells.

(Choices A and C) Decreased renal perfusion and glomerular filtration leads to decreased solute delivery to the juxtaglomerular apparatus in the distal tubule, which stimulates renin secretion by juxtaglomerular cells. Activation of the renin-angiotensin-aldosterone system leads to increased production of angiotensin II, a potent vasoconstrictor that preferentially constricts the efferent arteriole to restore glomerular filtration. These hormones do not have a substantial effect on red cell production.

(Choices B and E) Foot processes of renal podocytes surround glomerular capillaries to prevent filtration of large molecules (eg, plasma proteins); defects can cause chronic proteinuric kidney disease (eg, minimal change disease). Epithelial cells of the proximal tubule have a prominent role in reabsorption and secretion of solutes into the urine; these cells have high metabolic activity and are therefore susceptible to ischemic injury (eg, acute tubular necrosis) due to inadequate renal perfusion and oxygen delivery. However, neither of these cell types produces EPO.

Educational objective:
Erythropoietin (EPO) is produced primarily by peritubular fibroblast cells in the renal cortex in response to decreased renal oxygen delivery (eg, decreased blood hemoglobin content). EPO acts on erythrocyte precursor cells in the bone marrow to stimulate red blood cell production. Patients with chronic kidney disease have inflammatory damage to renal EPO-producing cells and often develop normocytic anemia due to insufficient EPO.

References

- Renal erythropoietin-producing cells in health and disease.

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References

- Renal erythropoietin-producing cells in health and disease.

Physiology	Renal, Urinary Systems & Electrolytes	Anemia of inflammation
Subject	System	Topic

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A 28-year-old man comes to the physician with muscle weakness and headaches for the last 2 months. He denies palpitations, tremors, or increased sweating. His blood pressure is 190/120 mm Hg and his pulse is 68/min. His serum potassium level is 2.8 mEq/L. The patient's plasma renin activity is high and his serum aldosterone levels are elevated. A 24-hour urine collection shows increased potassium excretion. Which of the following is the most likely cause of this patient's symptoms?

A. Adrenal cortical tumor
B. Adrenal medullary tumor
C. Juxtaglomerular cell tumor
D. Pituitary tumor
E. Primary hypertension

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- A. Adrenal cortical tumor (21%)
- B. Adrenal medullary tumor (5%)
- ✓ C. Juxtaglomerular cell tumor (64%)
- D. Pituitary tumor (4%)
- E. Primary hypertension (3%)

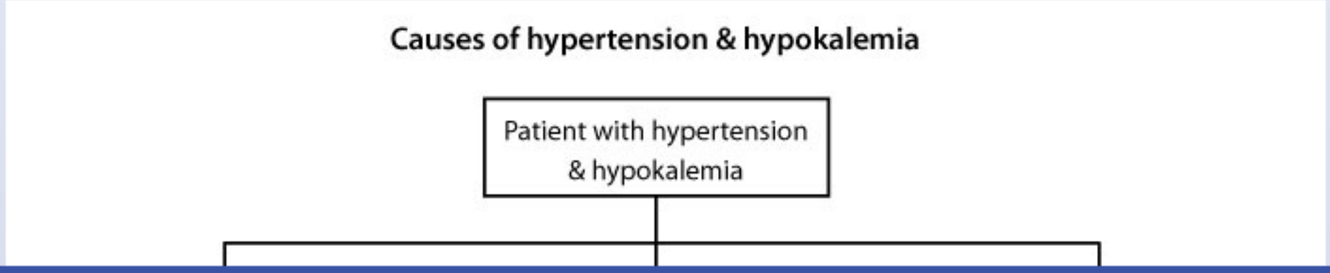
Omitted
Correct answer
C

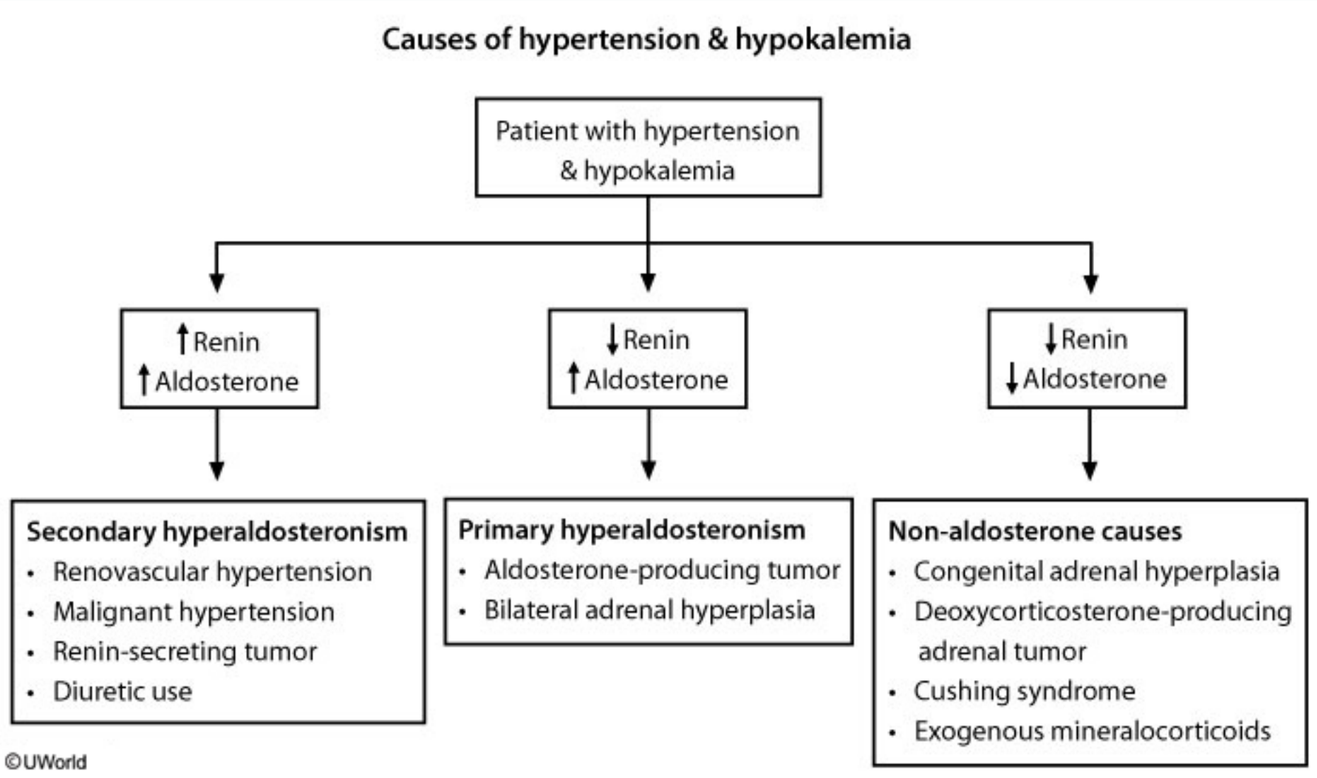
64%
Answered correctly

01 sec
Time Spent

04/09/2020
Last Updated

Explanation





This patient has **elevated serum aldosterone**, a known cause of hypertension, hypokalemia, and muscle weakness. Hyperaldosteronism can be divided into primary and secondary etiologies. In **primary hyperaldosteronism** (ie, Conn's syndrome), an adrenal adenoma or bilateral adrenal hyperplasia causes excessive and unchecked aldosterone production that leads to feedback inhibition of renin secretion (ie, **low renin** level). Primary hyperaldosteronism can be excluded in this patient due to his increased plasma renin activity **(Choice A)**.

In **secondary hyperaldosteronism**, overproduction of aldosterone occurs secondary to increased renin synthesis, resulting in **elevated renin** and aldosterone levels. Causes of secondary hyperaldosteronism include **renal artery stenosis** (typically associated with fibromuscular dysplasia or atherosclerosis), diuretic use, malignant hypertension (which leads to microvascular damage and renal ischemia), and renin-secreting tumors. Renin-secreting tumors (reninomas) are rare, small, solitary, benign **juxtaglomerular cell neoplasms**. Reninomas should be strongly considered

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(Choice B) Pheochromocytomas are adrenal medullary tumors that secrete excessive catecholamines. High epinephrine levels can sometimes cause hypokalemia via β2-receptor stimulation and the resulting intracellular K^+ shift. However, patients with pheochromocytomas typically present with episodic headaches, tachycardia (often sensed as palpitations), and increased sweating.

(Choice D) A pituitary tumor (eg, an ACTH-secreting adenoma causing Cushing's disease) can result in secondary hypertension due to excess adrenal glucocorticoids (increases vascular sensitivity to adrenergic agents). The resulting hypertension suppresses the renin-angiotensin-aldosterone axis, leading to low levels of renin and aldosterone.

(Choice E) Primary (essential) hypertension is not typically associated with severe hypertension, elevated levels of renin, or hypokalemia.

Educational objective:
Elevated serum aldosterone levels can manifest with hypertension, hypokalemia, and muscle weakness. Increased levels of both renin and aldosterone are indicative of secondary hyperaldosteronism, which can be caused by renovascular disease and renin-secreting tumors.

Physiology	Renal, Urinary Systems & Electrolytes	Hyperaldosteronism
Subject	System	Topic

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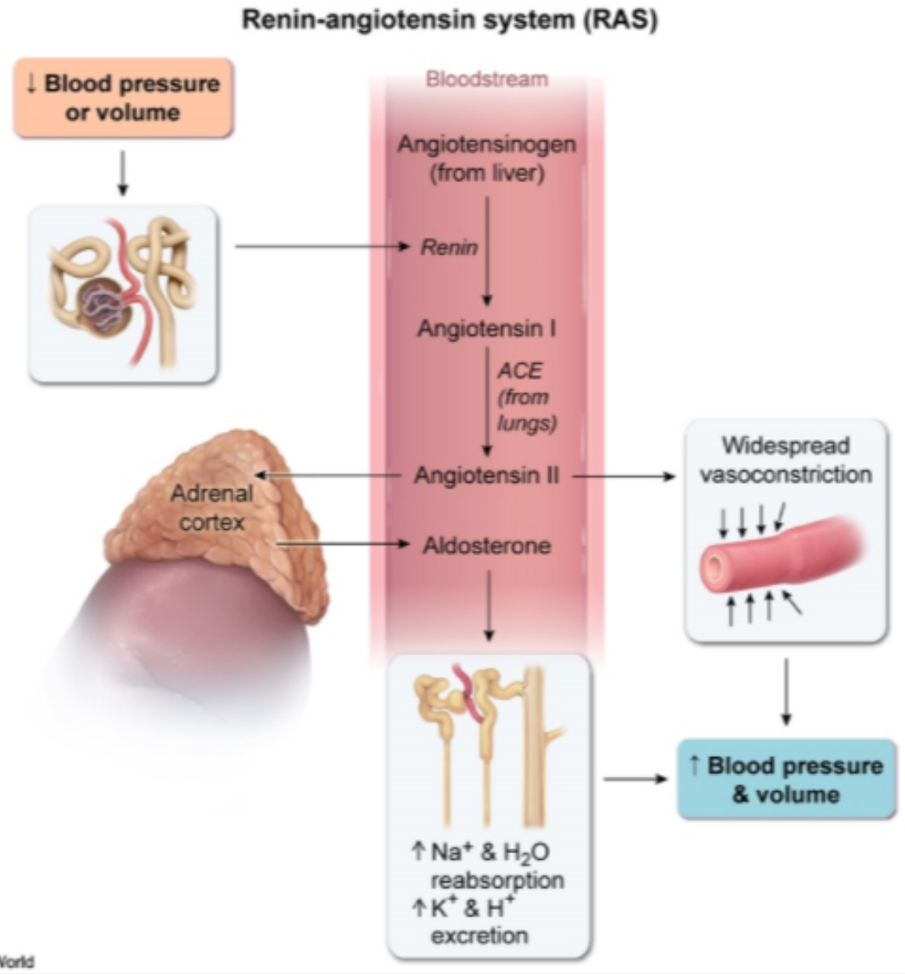

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A 44-year-old man comes to the hospital due to acute onset of central chest pain radiating to the left arm. He used cocaine a few hours ago. Blood pressure is 160/100 mm Hg, pulse is 98/min, and respirations are 18/min. On examination, the patient appears anxious and diaphoretic. Electrocardiogram shows ST-segment elevation in the anterior leads. Laboratory studies reveal an elevated cardiac troponin level and a serum potassium concentration of 3.1 mEq/L. Which of the following is the most likely cause of this patient's hypokalemia?

A. Decreased dietary potassium intake

B. Exchange of potassium with sodium in the intestine

C. Increased intracellular shift of potassium

D. Increased urinary loss of potassium

E. Increased use of potassium by new cells

Submit

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- A. Decreased dietary potassium intake (1%)
- B. Exchange of potassium with sodium in the intestine (3%)
- ✓ C. Increased intracellular shift of potassium (71%)
- D. Increased urinary loss of potassium (22%)
- E. Increased use of potassium by new cells (2%)

Omitted
Correct answer
C

71%
Answered correctly

02 secs
Time Spent

02/24/2020
Last Updated

Explanation

Causes of hypokalemia	
Decreased intake	• Starvation, anorexia
	• Insulin (eg, treatment of DKA, refeeding syndrome) • β-adrenergic activity ∘ Pharmacologic (eg, albuterol, dobutamine)

Causes of hypokalemia	
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Intracellular translocation	• Insulin (eg, treatment of DKA, refeeding syndrome)
	• β-adrenergic activity
	  ◦ Pharmacologic (eg, albuterol, dobutamine)
	  ◦ Stress-induced (eg, alcohol withdrawal, acute MI)
	• Alkalosis (respiratory or metabolic)
	• ↑ Cell reproduction (eg, acute myeloid leukemia, GM-CSF)

Gastrointestinal loss	• Diarrhea, vomiting, hyperaldosteronism
Urinary loss	• Hyperaldosteronism, diuretics, RTA types 1 and 2
Sweat loss	• Extreme exercise in hot climate

DKA = diabetic ketoacidosis; **MI** = myocardial infarction; **GM-CSF** = granulocyte-macrophage colony-stimulating factor; **RTA** = renal tubular acidosis.

Low serum potassium is a common medical condition that can result from several mechanisms, including decreased oral intake, renal or gastrointestinal loss, or increased entry into cells. This patient with a cocaine-induced **myocardial infarction** most likely developed **acute hypokalemia** due to stress-related **beta-adrenergic hyperactivity**, which causes potassium to shift intracellularly.

Severe physiologic stress (eg, myocardial infarction, head injury) results in significant endogenous catecholamine (eg, norepinephrine, epinephrine) release. Epinephrine activates the **beta-2 receptor**, leading to increased activity of the sodium-potassium ATPase pump and the sodium-potassium-2-chloride cotransporter, both of which **transport potassium intracellularly**. Adrenergic activity also stimulates the release of insulin, which further promotes intracellular potassium shifting. Although cocaine does not directly stimulate beta-2 receptors, it does increase catecholamine release, likely worsening hypokalemia.

Similar intracellular shifts can be seen with beta-agonist medications (eg, albuterol, dobutamine) and sympathomimetics (eg, pseudoephedrine). Patients with other sources of potassium loss (eg, diuretics, diarrhea) are at increased risk.

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(Choice A) Hypokalemia due to decreased dietary intake of potassium typically occurs in patients with very poor oral intake (eg, anorexia, starvation, malignancy).

(Choice B) Significant gastrointestinal potassium loss can occur with prolonged diarrhea or use of gastrointestinal cation exchangers that bind potassium in exchange for other cations (eg, sodium, calcium).

(Choice D) Increased urinary potassium loss can occur with diuretic use and in the setting of elevated aldosterone levels (eg, renovascular disease, primary aldosteronism). Although hyperaldosteronism is associated with hypertension, this patient's elevated blood pressure is likely from cocaine use.

(Choice E) Increased potassium uptake by cells during accelerated hematopoiesis (eg, administration of granulocyte-macrophage colony-stimulating factor, acute leukemia) may cause hypokalemia. However, this patient does not have these risk factors.

Educational objective:
Hypokalemia can result from the intracellular shift of potassium, which can occur due to beta-adrenergic hyperactivity (eg, beta-2 agonists, endogenous epinephrine release), increased insulin levels, elevated extracellular pH, or increased cell production (eg, acute leukemia).

Severe physiologic stress (eg, myocardial infarction, head injury) results in significant endogenous catecholamine (eg, norepinephrine, epinephrine) release. Epinephrine activates the **beta-2 receptor**, leading to increased activity of the sodium-potassium ATPase pump and the sodium-potassium-2-chloride cotransporter, both of which **transport potassium intracellularly**. Adrenergic activity also stimulates the release of insulin, which further promotes intracellular potassium shifting. Although cocaine does not directly stimulate beta-2 receptors, it does increase catecholamine release, likely worsening hypokalemia.

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Physiology	Renal, Urinary Systems & Electrolytes	Hypokalemia
Subject	System	Topic

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A clinical trial of a novel drug X is being conducted. Animal studies have shown that the drug is eliminated primarily by the kidneys. A healthy volunteer of body weight 60 kg (132.3 lb) is recruited, and his glomerular filtration rate is 100 mL/min. In this volunteer, plasma concentration of the drug, immediately after intravenous administration, is 0.5 mg/mL. Urinary excretion rate of the drug is found to be 75 mg/min. When another medication, drug Y, is coadministered, urinary excretion rate of the drug X is 50 mg/min. Which of the following effects of drug Y on the pharmacokinetics of drug X best explains the findings in this study?

A. Decreased renal tubular reabsorption

B. Decreased renal tubular secretion

C. Displacement from plasma proteins

D. Increased glomerular filtration

Submit

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- A. Decreased renal tubular reabsorption (4%)
- ✓ B. Decreased renal tubular secretion (88%)
- C. Displacement from plasma proteins (5%)
- D. Increased glomerular filtration (2%)

Omitted
Correct answer
B

88%
Answered correctly

01 sec
Time Spent

04/17/2020
Last Updated

Explanation

Renal excretion is a major mechanism of drug removal. This process is dependent on **glomerular filtration**, **tubular secretion,** and **tubular reabsorption** of the drug. Therefore, factors that reduce renal drug excretion and lead to increased plasma drug levels include the following:

- **Reduced glomerular filtration:** Kidney disease (eg, chronic kidney disease from diabetes mellitus) and reduced renal blood flow (eg, NSAID-induced vasoconstriction, volume contraction) lead to reduced drug filtration. In addition, plasma proteins are not filtered at the glomerulus; therefore, highly protein-bound drugs are not effectively filtered.
- **Reduced renal tubular secretion:** Active transport of drugs is largely dependent on transporters (eg, organic anion or cation transporter).

Explanation

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- **Reduced glomerular filtration:** Kidney disease (eg, chronic kidney disease from diabetes mellitus) and reduced renal blood flow (eg, NSAID-induced vasoconstriction, volume contraction) lead to reduced drug filtration. In addition, plasma proteins are not filtered at the glomerulus; therefore, highly protein-bound drugs are not effectively filtered.
- **Reduced renal tubular secretion:** Active transport of drugs is largely dependent on transporters (eg, organic anion or cation transporter). Coadministration of drugs with overlapping substrate specificity can result in competition for or inhibition of transporters.
- **Increased renal tubular reabsorption:** Only polarized (ionized) drugs are water soluble, whereas nonionized forms are lipid soluble and can passively diffuse across the renal tubular membrane to reenter the plasma. Therefore, alterations in urine pH can augment drug excretion; for example, acidification of urine favors the reabsorption of acidic drugs because a greater proportion of the drug is in the nonionized form.

The urinary excretion rate of drug X was reduced from 75 to 50 mg/min after the administration of drug Y. Of the options available, only **decreasing the renal tubular secretion** of drug X reduces is excretion rate. Drug Y likely had similar specificity for active transporters in the renal tubules, limiting or inhibiting the secretion of drug X.

(Choices A, C, and D) Decreased renal tubular reabsorption, displacement from plasma proteins, and increased glomerular filtration would all increase the excretion rate of drug X.

Educational objective:
Renal excretion of a drug is dependent on:

- Glomerular filtration (reduced with low renal blood flow, kidney disease, and high drug protein binding)
- Renal tubular secretion (reduced by coadministration of drugs with overlapping substrate specificity)
- Tubular reabsorption (may be altered by changes in urine pH)

Physiology Renal, Urinary Systems & Electrolytes Drug metabolism and clearance

- **Reduced glomerular filtration:** Kidney disease (eg, chronic kidney disease from diabetes mellitus) and reduced renal blood flow (eg, NSAID-induced vasoconstriction, volume contraction) lead to reduced drug filtration. In addition, plasma proteins are not filtered at the glomerulus; therefore, highly protein-bound drugs are not effectively filtered.
- **Reduced renal tubular secretion:** Active transport of drugs is largely dependent on transporters (eg, organic anion or cation transporter). Coadministration of drugs with overlapping substrate specificity can result in competition for or inhibition of transporters.
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(Choices A, C, and D) Decreased renal tubular reabsorption, displacement from plasma proteins, and increased glomerular filtration would all increase the excretion rate of drug X.

Educational objective:
Renal excretion of a drug is dependent on:

- Glomerular filtration (reduced with low renal blood flow, kidney disease, and high drug protein binding)
- Renal tubular secretion (reduced by coadministration of drugs with overlapping substrate specificity)
- Tubular reabsorption (may be altered by changes in urine pH)

Physiology	Renal, Urinary Systems & Electrolytes	Drug metabolism and clearance
Subject	System	Topic

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A healthy 32-year-old man enrolls in a clinical study investigating potassium handling by the kidney. During the study period, he is given oral potassium supplements and potassium levels in the serum and urine are closely monitored. Compared to the amount of potassium delivered to the glomerular capillaries, the percentage of potassium remaining in this individual's tubular fluid is most likely to vary by which of the following amounts?

	Bowman's capsule	End of proximal tubule	End of thick ascending limb of Henle's loop	End of collecting duct
A.	100%	35%	10%	110%
B.	100%	35%	70%	110%
C.	75%	50%	25%	110%
D.	100%	50%	100%	110%

Submit

A healthy 32-year-old man enrolls in a clinical study investigating potassium handling by the kidney. During the study period, he is given oral potassium supplements and potassium levels in the serum and urine are closely monitored. Compared to the amount of potassium delivered to the glomerular capillaries, the percentage of potassium remaining in this individual's tubular fluid is most likely to vary by which of the following amounts?

	Bowman's capsule	End of proximal tubule	End of thick ascending limb of Henle's loop	End of collecting duct
✓ A. (56%)	100%	35%	10%	110%
B. (29%)	100%	35%	70%	110%
C. (6%)	75%	50%	25%	110%
D. (7%)	100%	50%	100%	110%

Omitted
Correct answer
A

56%
Answered correctly

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Time Spent

04/27/2020
Last Updated

Explanation

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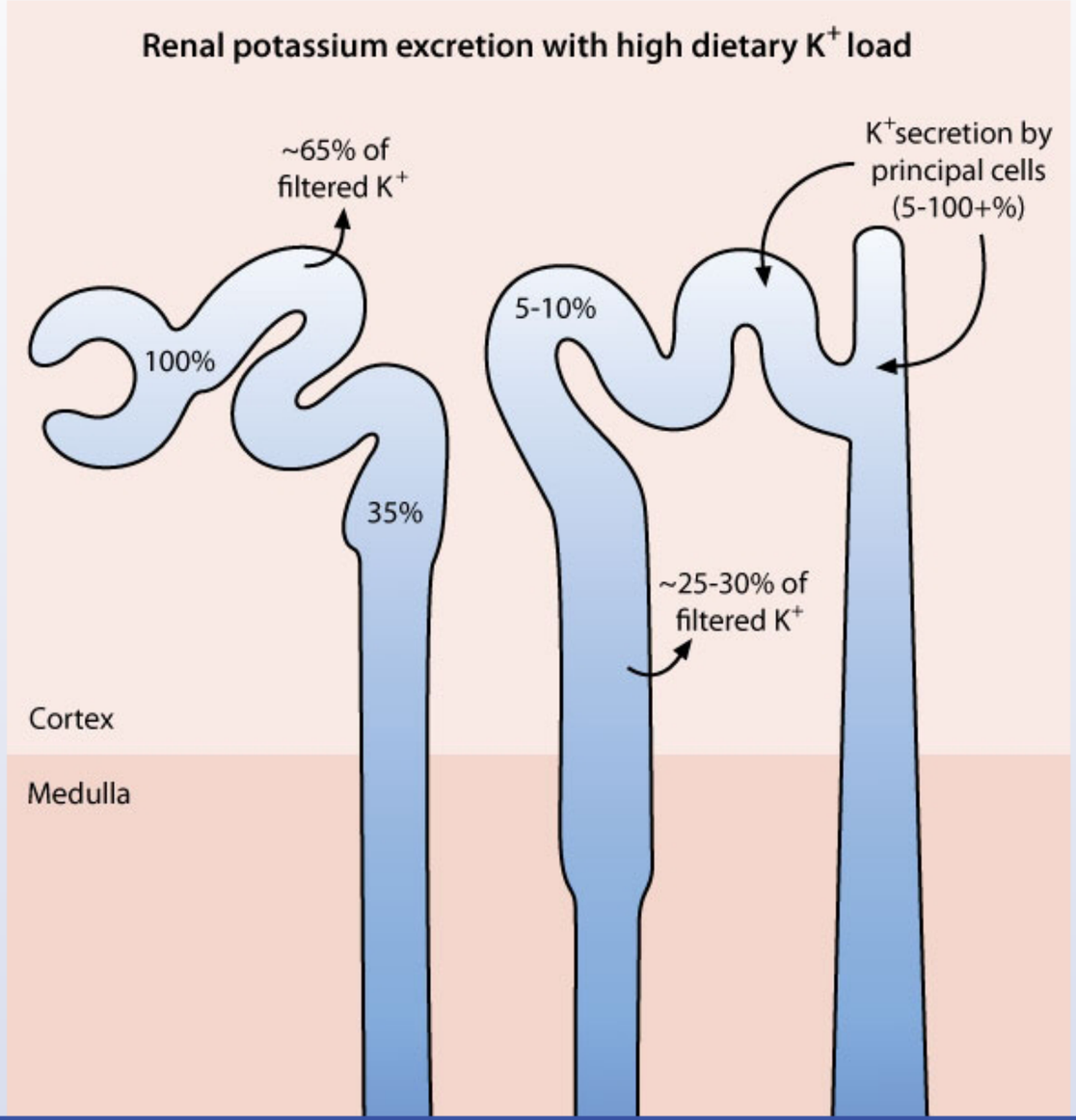

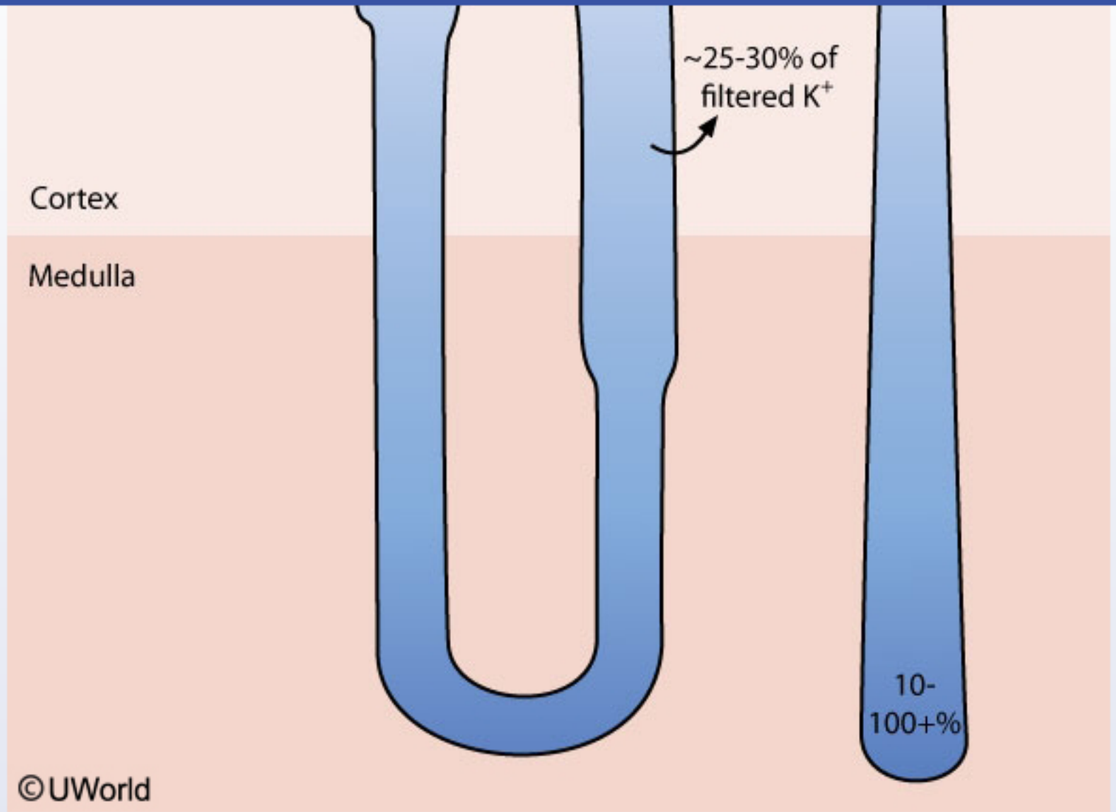

Several segments of the nephron are involved in the management of potassium (K^+). However, most handle K^+ at a relatively fixed rate that is independent of potassium load and do not play a significant role in the regulation of K^+ excretion in the urine. These segments include the following:

- Bowman's capsule: Because **K^+ is freely filtered** across the glomerular membrane, the amount of K^+ within Bowman's space is equal to that in the glomerular capillaries (ie, 100%) **(Choice C)**.
- The proximal tubule: Approximately 65% of the filtered K^+ load is reabsorbed in the proximal tubule, leaving **~35%** of the total filtered load.
- The thick ascending limb of the loop of Henle: Further resorbs about 25%-30% of the filtered K^+ load through the action of the $Na^+/K^+/2Cl^-$ cotransporter, resulting in only **5-10% of K^+** remaining in the tubular fluid after this segment **(Choices B and D)**.

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Several segments of the nephron are involved in the management of potassium (K^+). However, most handle K^+ at a relatively fixed rate that is independent of potassium load and do not play a significant role in the regulation of K^+ excretion in the urine. These segments include the following:

- Bowman's capsule: Because **K^+ is freely filtered** across the glomerular membrane, the amount of K^+ within Bowman's space is equal to that in the glomerular capillaries (ie, 100%) **(Choice C)**.
- The proximal tubule: Approximately 65% of the filtered K^+ load is reabsorbed in the proximal tubule, leaving **~35%** of the total filtered load.
- The thick ascending limb of the loop of Henle: Further resorbs about 25%-30% of the filtered K^+ load through the action of the $Na^+/K^+/2Cl^-$ cotransporter, resulting in only **5-10% of K^+** remaining in the tubular fluid after this segment **(Choices B and D)**.

Because this is a stable process, even in hyperkalemic states, patients will **reabsorb the majority of filtered K^+** in the **proximal tubule** and **loop of Henle.**

Potassium regulation is therefore primarily mediated by the principal and α-intercalated cells of the late distal and cortical collecting tubules. Hypokalemia stimulates reabsorption of K^+ via apically located H^+/K^+-ATPases on α-intercalated cells and can cause the amount of K^+ in the collecting tubule to approach 1% of the filtered load. Conversely, an **increased K^+ load** stimulates principal cells to secrete K^+ through apical K^+ channels. High dietary K^+ intake can cause the amount of K^+ in the **collecting tubules** to actually exceed the filtered load (ie, **>100%**).

Excessive K^+ intake increases K^+ excretion through the following mechanisms:

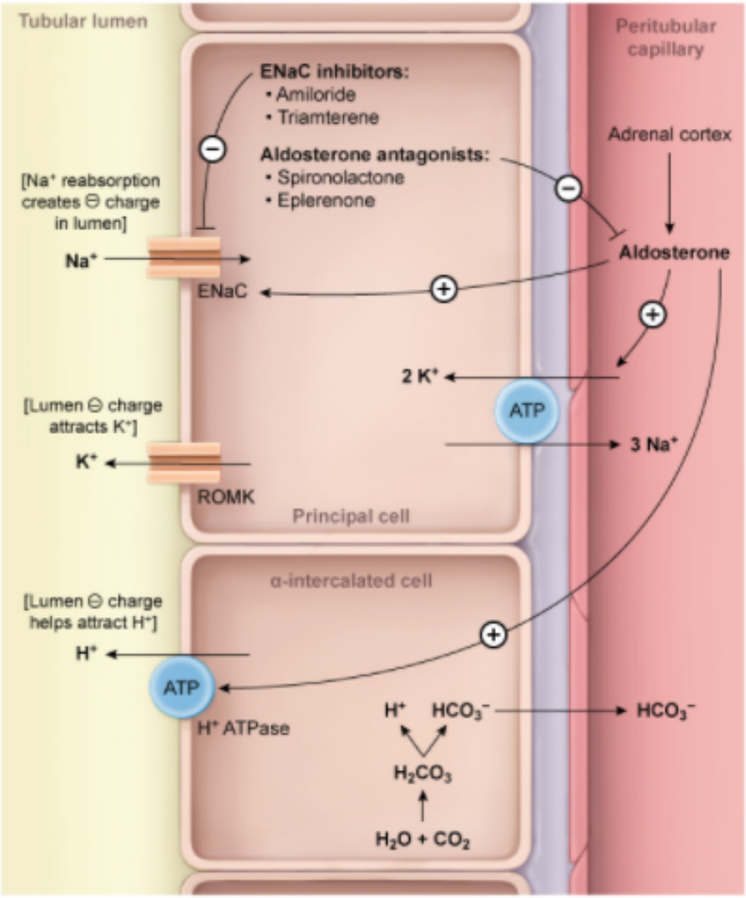
- High extracellular K^+ levels directly stimulate basolateral Na^+/K^+ pumps on principal cells, increasing K^+ secretion into the tubular fluid.
- Elevated K^+ levels also increase aldosterone secretion, which further enhances activity of principal cell Na^+/K^+ pumps and also increases their apical permeability to Na^+ and K^+ (leading to K^+ loss in the tubular fluid).

Educational objective:
K^+ is freely filtered by the glomeruli and is mostly reabsorbed in the proximal tubule and loop of Henle. As such, the late distal and cortical collecting tubules are the primary sites for regulation of K^+ excretion in the urine. K^+ depletion stimulates α-intercalated cells to reabsorb extra potassium; principal cells secrete K^+ under conditions of increased K^+ load.

- Bowman's capsule: Because **K^+ is freely filtered** across the glomerular membrane, the amount of K^+ within Bowman's space is equal to

Exhibit Display

Action of aldosterone in the collecting duct of the nephron



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A researcher is studying the effect of various manipulations on kidney blood flow and glomerular filtration. Which of the following is most likely to both decrease renal plasma flow and increase the filtration fraction?

A. Hyperproteinemia

B. Bladder neck obstruction

C. Constriction of the efferent arteriole

D. Constriction of the afferent arteriole

E. Dilation of the efferent arteriole

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A researcher is studying the effect of various manipulations on kidney blood flow and glomerular filtration. Which of the following is most likely to both decrease renal plasma flow and increase the filtration fraction?

- A. Hyperproteinemia (1%)
- B. Bladder neck obstruction (1%)
- ✓ C. Constriction of the efferent arteriole (82%)
- D. Constriction of the afferent arteriole (11%)
- E. Dilation of the efferent arteriole (2%)

Omitted
Correct answer
C

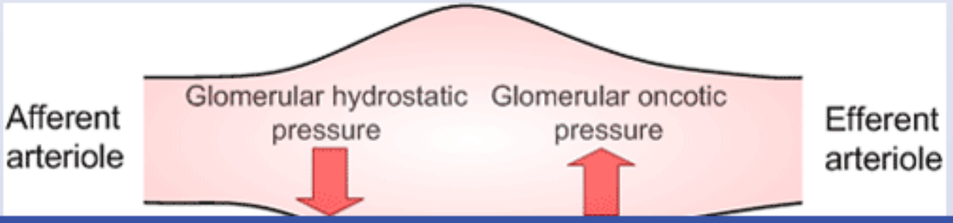
82%
Answered correctly

02 secs
Time Spent

02/03/2020
Last Updated

Explanation

Constriction of the efferent (outgoing) arteriole will impede blood flow through the kidney. This will decrease RPF, but will increase glomerular capillary hydrostatic pressure as the fluid "backs up" in the glomerulus, increasing hydrostatic pressure. As described below, this increased glomerular hydrostatic pressure will cause an increase in the filtration fraction.



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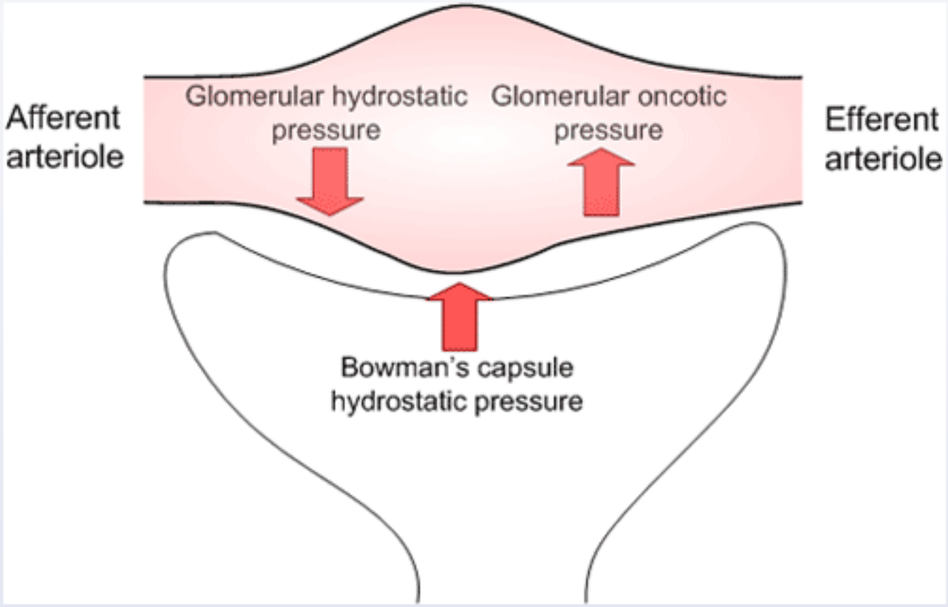
Explanation

Constriction of the efferent (outgoing) arteriole will impede blood flow through the kidney. This will decrease RPF, but will increase glomerular capillary hydrostatic pressure as the fluid "backs up" in the glomerulus, increasing hydrostatic pressure. As described below, this increased glomerular hydrostatic pressure will cause an increase in the filtration fraction.



The renal plasma flow (RPF) is the volume of plasma that is delivered to the kidney per unit time. The RPF is provided by the renal blood flow, which delivers both erythrocytes and plasma to the kidney. The RPF is theoretically calculated by subtracting the amount of erythrocytes (hematocrit) from the total renal blood flow. Clinically, however, RPF is generally estimated by calculating the paraaminohippuric acid (PAH) clearance. RPF is linked to the glomerular filtration rate (GFR) and the filtration fraction (FF) by the following equation:

$$FF = GFR / RPF$$

The filtration fraction refers to the proportion of the RPF that is filtered from the glomerular capillaries into Bowman's space and is expressed as a

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$$FF = GFR / RPF$$

The filtration fraction refers to the proportion of the RPF that is filtered from the glomerular capillaries into Bowman's space and is expressed as a percentage. Using the equation above, one can observe that increases in GFR or decreases in RPF will increase the FF. The GFR is dependent on hydrostatic and oncotic pressures in the glomerular capillaries and Bowman's space and can be calculated with the following equation:

$$GFR = K_f ((P_G - P_B) - (\pi_G - \pi_B))$$

Where Kf refers to the coefficient of filtration, P_G refers to the hydrostatic pressure in the glomerular capillaries, P_B refers to the hydrostatic pressure in Bowman's space, π_G refers to the oncotic pressure in the glomerular capillaries and π_B refers to the oncotic pressure in Bowman's space. Increases in the glomerular capillary hydrostatic pressure or the Bowman's space oncotic pressure will increase GFR, while increases in capillary oncotic pressure or Bowman's space hydrostatic pressure will decrease GFR.

(Choice A) Hyperproteinemia causes increased glomerular capillary oncotic pressure thereby decreasing GFR. This will have no effect on the RPF, but will cause a decreased FF due to the decreased GFR.

(Choice B) Bladder neck obstruction causes an increase in Bowman's space hydrostatic pressure thereby decreasing GFR. This too will have no effect on the RPF, but will cause a decreased FF due to the decreased GFR.

(Choice D) Constriction of the afferent (incoming) arteriole causes a decrease in glomerular capillary hydrostatic pressure leading to a decreased GFR. RPF is also decreased by this process. The FF remains unchanged due to decreases in both GFR and RPF.

(Choice E) Dilation of the efferent arteriole causes decreased glomerular capillary hydrostatic pressure leading to a decrease in GFR. The RPF is increased by this process, and the FF is decreased due to the decrease in GFR and increase in RPF.

Educational Objective:

percentage. Using the equation above, one can observe that increases in GFR or decreases in RPF will increase the FF. The GFR is dependent on hydrostatic and oncotic pressures in the glomerular capillaries and Bowman's space and can be calculated with the following equation:

$$GFR = K_f ((P_G - P_B) - (\pi_G - \pi_B))$$

Where Kf refers to the coefficient of filtration, P_G refers to the hydrostatic pressure in the glomerular capillaries, P_B refers to the hydrostatic pressure in Bowman's space, π_G refers to the oncotic pressure in the glomerular capillaries and π_B refers to the oncotic pressure in Bowman's space. Increases in the glomerular capillary hydrostatic pressure or the Bowman's space oncotic pressure will increase GFR, while increases in capillary oncotic pressure or Bowman's space hydrostatic pressure will decrease GFR.

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(Choice D) Constriction of the afferent (incoming) arteriole causes a decrease in glomerular capillary hydrostatic pressure leading to a decreased GFR. RPF is also decreased by this process. The FF remains unchanged due to decreases in both GFR and RPF.

(Choice E) Dilation of the efferent arteriole causes decreased glomerular capillary hydrostatic pressure leading to a decrease in GFR. The RPF is increased by this process, and the FF is decreased due to the decrease in GFR and increase in RPF.

Educational Objective:
Increases in the capillary hydrostatic pressure or the Bowman's space oncotic pressure will increase GFR, while increases in capillary oncotic pressure or Bowman's space hydrostatic pressure will decrease GFR. The filtration fraction (FF) can be calculated by dividing the GFR by the renal plasma flow (RPF). Increases in GFR or decreases in RPF will increase the FF.

Physiology	Renal, Urinary Systems & Electrolytes	GFR
Subject	System	Topic

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A 43-year-old man comes to the office due to swelling of the legs and abdomen. The patient has a history of alcoholic cirrhosis, and his ascites had been well controlled with furosemide. Over the past week, he has had increasing bilateral lower extremity and abdominal swelling despite taking a diuretic as prescribed. The patient reports no change in dietary sodium or water intake but states he has been taking over-the-counter ibuprofen after injuring his back recently. He stopped drinking alcohol 2 years ago and does not use tobacco or illicit drugs. Physical examination shows 3+ bilateral lower extremity edema and moderate ascites. Which of the following changes most likely contributed to the acute deterioration in this patient's condition?

	Renal prostaglandin level	Glomerular filtration rate	Urinary sodium excretion
A.	Decreased	Decreased	Decreased
B.	Decreased	Unchanged	Decreased
C.	Increased	Increased	Increased
D.	Increased	Increased	Unchanged
E.	Unchanged	Decreased	Increased

Submit

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	Renal prostaglandin level	Glomerular filtration rate	Urinary sodium excretion
✓ A. (88%)	Decreased	Decreased	Decreased
B. (5%)	Decreased	Unchanged	Decreased
C. (1%)	Increased	Increased	Increased
D. (1%)	Increased	Increased	Unchanged
E. (2%)	Unchanged	Decreased	Increased

Omitted
Correct answer
A

88%
Answered correctly

02 secs
Time Spent

06/18/2020
Last Updated

Explanation

Furosemide is a loop diuretic that binds to Na-K-2Cl symporters in the ascending limb of the loop of Henle and effectively blocks Na and Cl transport, resulting in increased Na, Cl, and fluid excretion. Loop diuretics also **stimulate prostaglandin release**, which increases renal plasma flow (RPF), leading to increased glomerular filtration rate (GFR) and drug delivery to the loop of Henle.

Nonsteroidal anti-inflammatory drugs (NSAIDs) (eg, ibuprofen, naproxen, indomethacin) **inhibit prostaglandin synthesis** (resulting in decreased renal prostaglandin levels). In healthy patients, prostaglandin synthesis is low and NSAID use has minimal effects on renal hemodynamics. However, patients with intravascular volume depletion (eg, **cirrhosis**, congestive heart failure, dehydration) are dependent on the vasodilatory effects of prostaglandins to maintain adequate RPF and GFR.

Therefore, NSAID use in this population leads to markedly **decreased GFR and RPF**. Reduced fluid and electrolyte delivery to renal tubules reduces the efficacy of loop diuretics, resulting in **reduced urinary sodium excretion** and fluid retention (eg, ascites, edema, as occurred in this patient). Similar effects can occur in patients with chronic kidney disease; therefore, NSAIDs should generally be avoided in all patients with renal disease or reduced effective arterial volume.

(Choices B, C, D, and E) NSAIDs inhibit prostaglandin synthesis, resulting in renal vasoconstriction and decreased GFR. This limits the efficacy of loop diuretics, leading to reduced urinary sodium excretion and fluid retention (promoting the formation of ascites and edema).

Educational objective:
Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin synthesis. Patients with intravascular volume depletion (eg, cirrhosis) are dependent on the vasodilatory effects of prostaglandins to maintain adequate renal plasma flow and glomerular filtration. NSAID use in this population reduces glomerular filtration rates and blunts the effects of loop diuretics, leading to sodium and water retention.

Physiology	Renal, Urinary Systems & Electrolytes	Loop diuretics
Subject	System	Topic

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Physiologists are studying the forces governing glomerular ultrafiltration using a single nephron in an intact kidney of an experimental animal. Hydrostatic pressure in the glomerular capillary and Bowman space is measured using micropipette transducers. Colloid osmotic pressure in the glomerular capillary is estimated using the difference in plasma protein concentration in the afferent and efferent arterioles. The glomerular surface is assumed to be functionally intact with negligible filtration of plasma proteins into the Bowman space. From the data obtained, net filtration pressure is calculated at 10 mm Hg. A substance is instilled into the renal artery, and measurements are repeated. The net filtration pressure after the intervention is 20 mm Hg. Which of the following substances was most likely used in this experiment?

- A. Albumin concentrate
- B. Alpha-adrenergic agonist
- C. Angiotensin II agonist
- D. Prostaglandin inhibitor
- E. Vasopressin 2 antagonist

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A. Albumin concentrate (4%)
B. Alpha-adrenergic agonist (4%)
✓ C. Angiotensin II agonist (79%)
D. Prostaglandin inhibitor (6%)
E. Vasopressin 2 antagonist (3%)

Omitted
Correct answer
C

79%
Answered correctly

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05/27/2020
Last Updated

Explanation

Net filtration pressure in the glomerulus

Net filtration pressure = $[P_c - P_i] - [\pi_c - \pi_i]$

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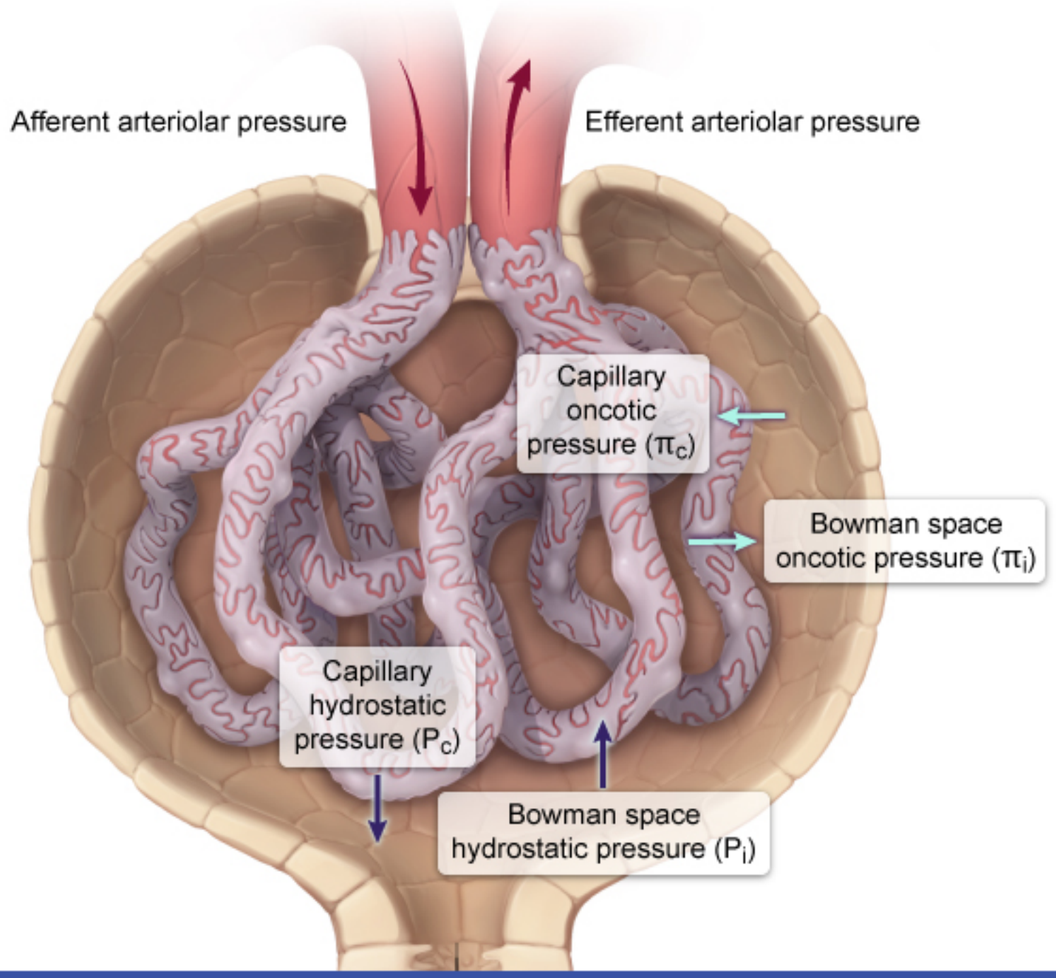
Net filtration pressure in the glomerulus

Net filtration pressure = $[P_c - P_i] - [\pi_c - \pi_i]$



Net filtration pressure

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The net filtration pressure is a result of pressure gradients formed by Starling forces and is calculated by subtracting the oncotic pressure gradient from the hydrostatic pressure gradient (ie, net filtration pressure = $[P_c - P_i] - [\pi_c - \pi_i]$):

- **The hydrostatic pressure gradient** ($P_c - P_i$) is the difference between the hydrostatic pressure in the intraglomerular capillaries and Bowman's space. Hydrostatic pressure in the capillaries is higher than in Bowman's space, and provides the **driving force for fluid efflux** from the capillaries.
- **The oncotic pressure gradient** ($\pi_c - \pi_i$) is the difference between the oncotic pressure in the intraglomerular capillaries and Bowman's space. Oncotic pressure is driven chiefly by large plasma proteins (eg, albumin), which do not freely filter across the glomerular capillary basement membrane due to both a size and a charge barrier. The high oncotic pressure in the capillaries counteracts the capillary hydrostatic pressure and **decreases net fluid efflux** from the capillaries.

This patient's net **filtration pressure has increased** from 10 to 20 mm Hg after infusion of a substance. Increased net filtration pressure occurs due to either an increase in the hydrostatic pressure gradient or a decrease in the oncotic pressure gradient. Of the available options, only an **angiotensin II agonist** would increase the net filtration pressure. Angiotensin II preferentially **constricts the efferent arteriole**, resulting in an **increased hydrostatic pressure gradient** and increased net filtration pressure.

(Choice A) Albumin is not filtered across the glomerular capillary and would increase the oncotic pressure gradient, resulting in a lower net filtration pressure.

(Choice B) Alpha-1 receptors are located mainly in the afferent arteriole; alpha agonists (eg, epinephrine, norepinephrine) result in constriction of the afferent arteriole, which reduces hydrostatic pressure and leads to lower net filtration pressures.

(Choice D) Prostaglandins (eg, prostaglandin E2) are responsible for dilation of the afferent arteriole. Inhibition of prostaglandin synthesis, as seen with nonsteroidal anti-inflammatory drugs, results in constriction of the afferent arteriole, leading to reduced hydrostatic pressure and a lower net filtration pressure.

(Choice E) Vasopressin 2 antagonists (eg, tolvaptan) reduce vasopressin-induced free water resorption. These drugs do not have a direct effect on the Starling forces; however, reduced free water resorption can result in decreased blood volume, which decreases capillary hydrostatic pressure, which would lower the net filtration pressure.

basement membrane due to both a size and a charge barrier. The high oncotic pressure in the capillaries counteracts the capillary hydrostatic pressure and **decreases net fluid efflux** from the capillaries.

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(Choice E) Vasopressin 2 antagonists (eg, tolvaptan) reduce vasopressin-induced free water resorption. These drugs do not have a direct effect on the Starling forces; however, reduced free water resorption can result in decreased blood volume, which decreases capillary hydrostatic pressure, which would lower the net filtration pressure.

Educational objective:
The net filtration pressure is a result of pressure gradients formed by Starling forces and is calculated by subtracting the oncotic pressure gradient from the hydrostatic pressure gradient. Angiotensin II preferentially constricts the efferent arteriole, resulting in an increased hydrostatic pressure gradient and an increased net filtration pressure.

Physiology	Renal, Urinary Systems & Electrolytes	GFR
Subject	System	Topic

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A 23-year-old man with a history of type 1 diabetes mellitus is brought to the emergency department due to confusion and weakness. His symptoms began 2 days ago after he started having mild diarrhea. He has missed several doses of insulin because his appetite has been poor. On examination, his breath has a fruity odor. This patient is most likely to demonstrate which of the following urine chemistry patterns?

	pH	HCO_3^-	$H_2PO_4^-$
A.	↑	↑	↑
B.	↑	↓	↑
C.	↓	↓	↓
D.	↓	↓	↑
E.	↓	↑	↑

Submit

A 23-year-old man with a history of type 1 diabetes mellitus is brought to the emergency department due to confusion and weakness. His symptoms began 2 days ago after he started having mild diarrhea. He has missed several doses of insulin because his appetite has been poor. On examination, his breath has a fruity odor. This patient is most likely to demonstrate which of the following urine chemistry patterns?

	pH	HCO_3^-	$H_2PO_4^-$
A. (5%)	↑	↑	↑
B. (4%)	↑	↓	↑
C. (21%)	↓	↓	↓
✓ D. (57%)	↓	↓	↑
E. (10%)	↓	↑	↑

Omitted
Correct answer
D

57%
Answered correctly

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Explanation

Renal acid excretion

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Renal acid excretion

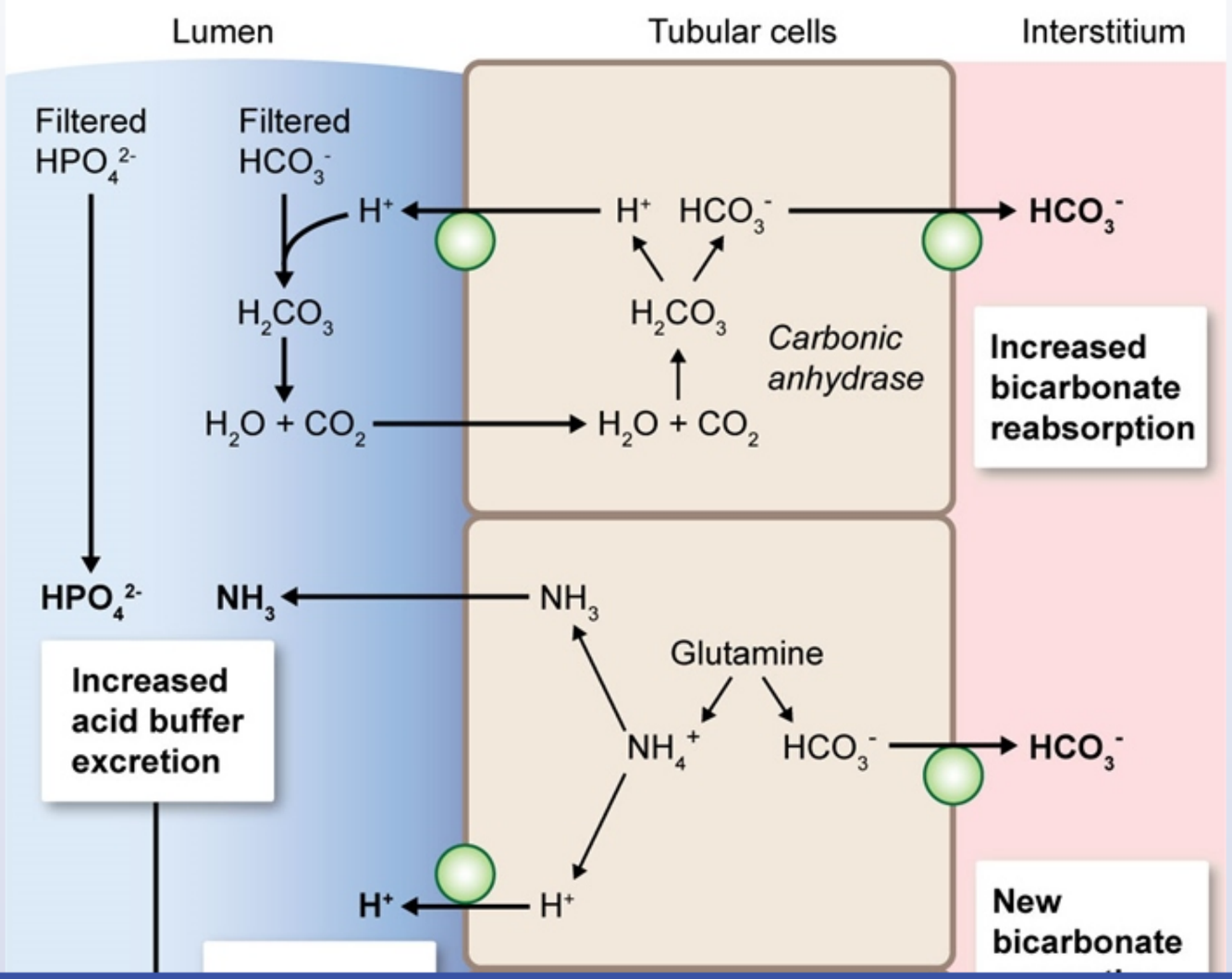

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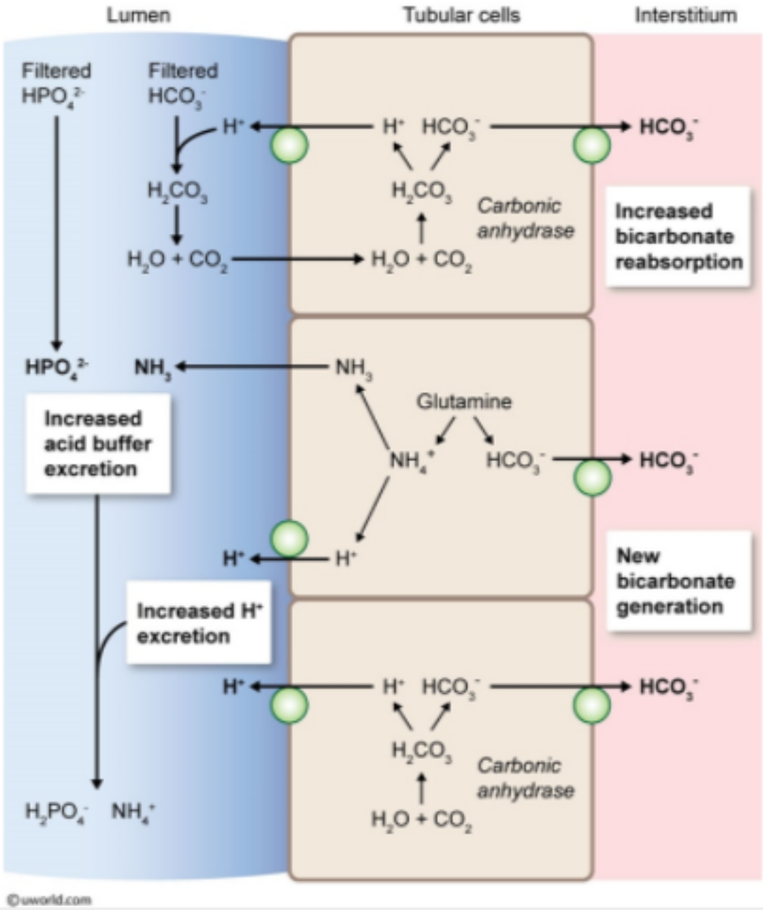
Exhibit Display

Renal acid excretion



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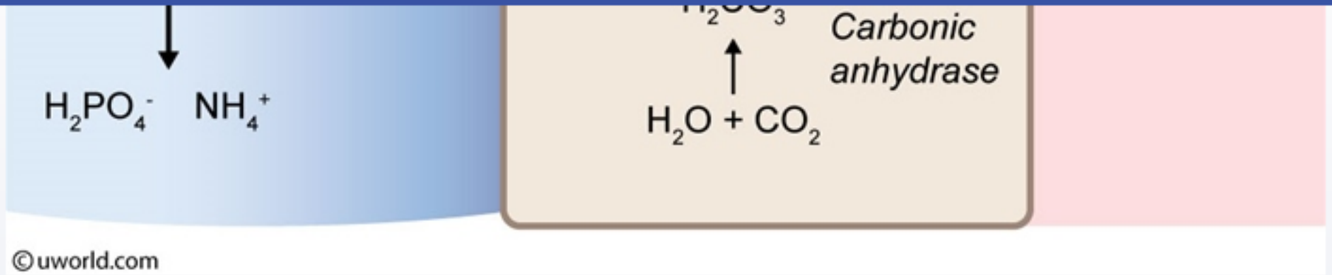

This patient has **diabetic ketoacidosis**, which (like other forms of metabolic acidosis) is characterized by decreased serum pH and bicarbonate (HCO_3^-) with a compensatory decrease in pCO_2. The kidneys try to correct metabolic acidosis via 3 major mechanisms:

1. **Increased HCO_3^- reabsorption:** Carbonic anhydrase in the proximal tubular lumen facilitates reabsorption of filtered HCO_3^-. Each reabsorbed HCO_3^- is equivalent to secretion of a H^+. In states of metabolic acidosis, HCO_3^- is completely reabsorbed from the tubular fluid.
2. **Increased H^+ secretion:** Acidosis increases H^+ secretion throughout the nephron. However, pH changes rapidly with relatively small changes in H^+ concentration, limiting the amount of acid that can be secreted as free H^+ in the urine.
3. **Increased acid buffer excretion:** In order to facilitate excretion of much larger amounts of acid, the kidney utilizes acid buffers to trap H^+ without markedly lowering urinary pH. The 2 most important acid buffers in urine are hydrogen phosphate (HPO_4^{2-}) and ammonia (NH_3), which combine with secreted H+ to form $H_2PO_4^-$ and NH_4^+. In chronic acidosis, proximal tubular cells greatly increase production of NH_3 to increase acid excretion.

Educational objective:
The kidneys compensate for metabolic acidosis by completely reabsorbing filtered bicarbonate (HCO_3^-) and excreting excess H^+ in the urine. Most of the excreted H^+ is buffered by phosphate ($H_2PO_4^-$) and ammonium (NH_4^+), which allows for large amounts of acid to be excreted without precipitously dropping the pH.

Physiology	Renal, Urinary Systems & Electrolytes	Diabetic ketoacidosis
Subject	System	Topic

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A 38-year-old man is brought to the emergency department due to progressive nausea, confusion, and unsteady gait. Family members state that symptoms started 4 days ago after he went to the dentist due to a toothache, for which he was prescribed ibuprofen. He also takes lithium for bipolar disorder. On examination, he is drowsy and ataxic, having slurred speech and coarse tremors. His serum lithium level is 3.86 mEq/L (therapeutic range: 0.8-1.2 mEq/L), and serum creatinine and blood urea nitrogen are elevated. While in the emergency department, he develops a generalized tonic-clonic seizure. During emergent hemodialysis treatment, his blood is passed along a semipermeable membrane and allowed to equilibrate with a dialysate solution. Which of the following is most likely to increase the rate of drug removal?

A. Adding lithium to the dialysis solution

B. Decreasing dialysis solution temperature

C. Decreasing the membrane pore size

D. Increasing surface area of the membrane

E. Increasing thickness of the membrane

Submit

A 38-year-old man is brought to the emergency department due to progressive nausea, confusion, and unsteady gait. Family members state that symptoms started 4 days ago after he went to the dentist due to a toothache, for which he was prescribed ibuprofen. He also takes lithium for bipolar disorder. On examination, he is drowsy and ataxic, having slurred speech and coarse tremors. His serum lithium level is 3.86 mEq/L (therapeutic range: 0.8-1.2 mEq/L), and serum creatinine and blood urea nitrogen are elevated. While in the emergency department, he develops a generalized tonic-clonic seizure. During emergent hemodialysis treatment, his blood is passed along a semipermeable membrane and allowed to equilibrate with a dialysate solution. Which of the following is most likely to increase the rate of drug removal?

- A. Adding lithium to the dialysis solution (1%)
- B. Decreasing dialysis solution temperature (1%)
- C. Decreasing the membrane pore size (3%)
- ✓ D. Increasing surface area of the membrane (92%)
- E. Increasing thickness of the membrane (1%)

Omitted
Correct answer
D

92%
Answered correctly

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Explanation

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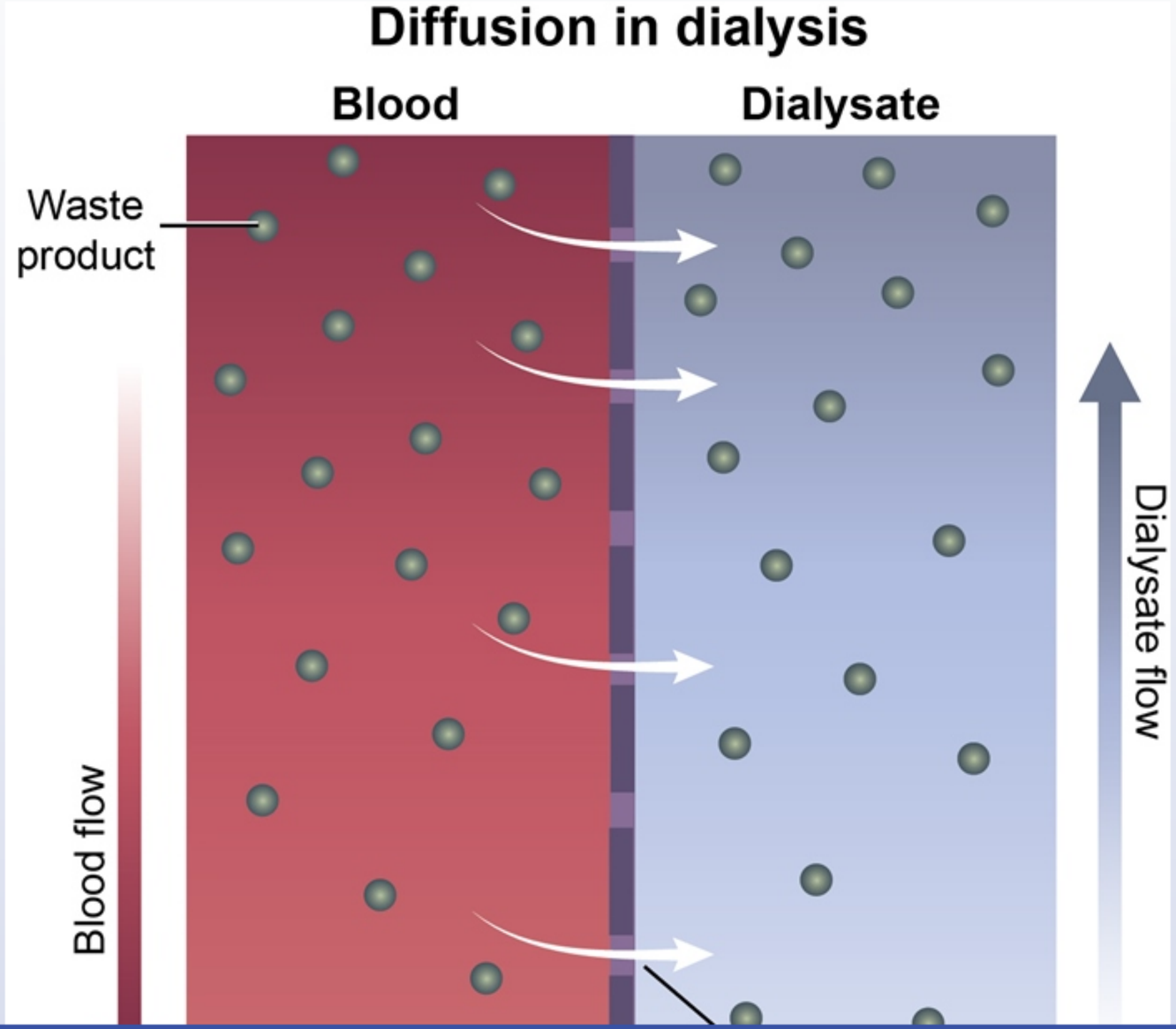

Diffusion in dialysis

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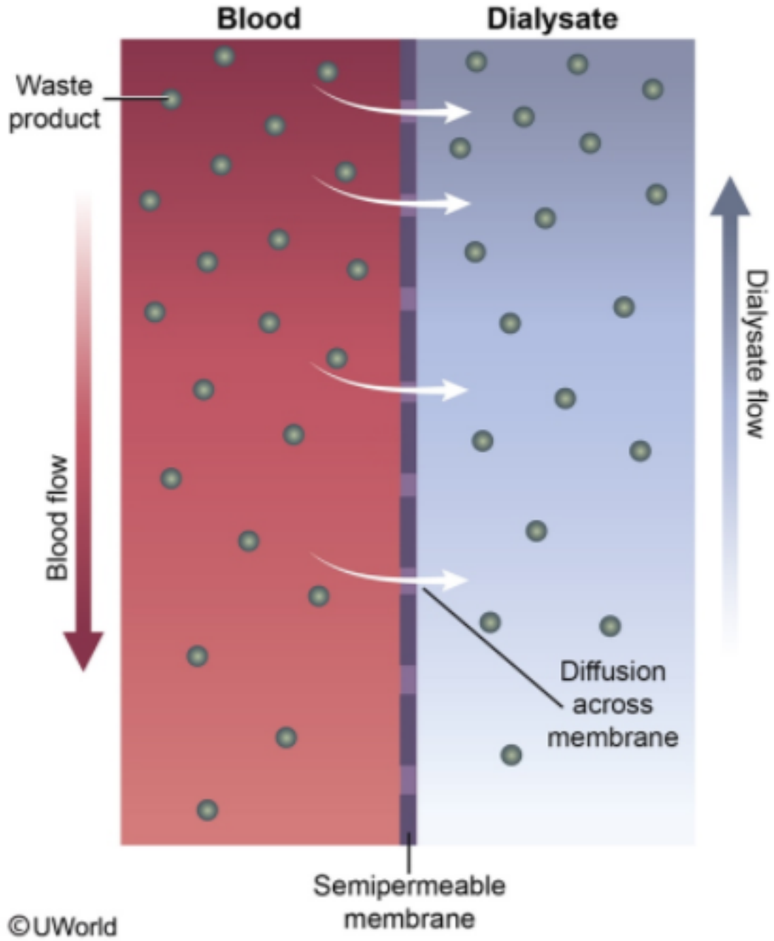
Diffusion in dialysis



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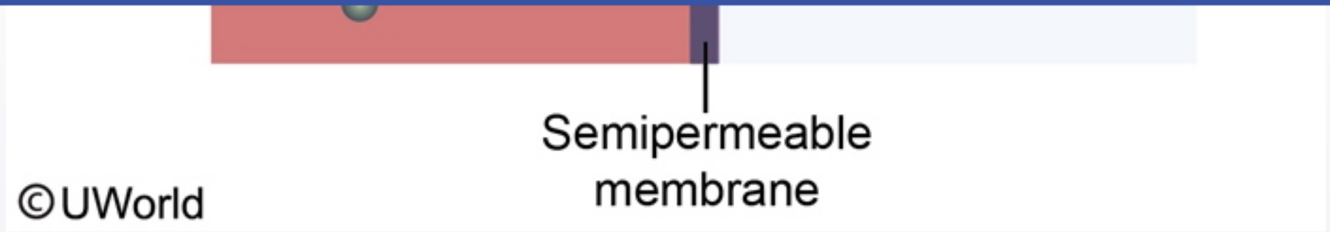

This patient is presenting with severe lithium toxicity secondary to his recent NSAID use and requires urgent hemodialysis to lower his blood lithium levels. Multiple factors affect the rate of **molecular diffusion** across a semipermeable membrane separating 2 well-mixed compartments. The number of molecules that cross the membrane per second is **proportional** to the molecular **concentration difference** across the membrane, the **surface area** of the membrane, and the solubility of the substance. Diffusion is inversely proportional to the total membrane thickness and the molecular weight of the molecule.

(Choice A) Adding lithium to the dialysate will decrease the concentration gradient between the dialysate and the patient's plasma. This would decrease the diffusion rate of lithium across the membrane.

(Choice B) Diffusion rate generally increases with temperature due to increased molecular movement speed and increased macromolecule solubility.

(Choices C and E) A decrease in membrane pore size would slow or prevent diffusion of larger molecules across the membrane. Increasing membrane thickness would also decrease diffusion rate.

Educational objective:
Diffusion speed across a semipermeable membrane increases with higher molecular concentration gradients, larger membrane surface areas, and increased solubility of the diffusing substance. Diffusion speed decreases with increased membrane thickness, smaller pore size, higher molecular weights, and lower temperatures.

Physiology	Renal, Urinary Systems & Electrolytes	Lithium
Subject	System	Topic

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This patient is presenting
lithium levels. Multiple fac
The number of molecules
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(Choice A) Adding lithiun
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(Choice B) Diffusion rate
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(Choices C and E) A dec
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Educational objective:
Diffusion speed across a s
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Lithium toxicity	

Etiology	Acute toxicity
	• Intentional overdose
	Chronic toxicity
	• Decreased renal perfusion (↓ lithium clearance)
	  ◦ Dehydration
	  ◦ Thiazide diuretics, NSAIDs, ACE inhibitors

Clinical features	Acute toxicity • **Gastrointestinal**: nausea, vomiting, diarrhea • Late neurologic sequelae Chronic toxicity **(neurologic)** • Lethargy, confusion, agitation • Ataxia, tremor/fasciculations, seizure
Treatment	• Intravenous hydration • Hemodialysis (severe cases)

NSAID = nonsteroidal anti-inflammatory drug.

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A 24-year-old man who lives at an elevation near sea-level goes hiking in the Colorado mountains and ascends to an altitude of 4,000 m (13,123 ft). He stays on the mountain overnight and develops diffuse headache, nausea, and difficulty sleeping. The patient also notes mild fatigue and slight dizziness with changes in position. He has no medical conditions and currently takes no medications. He does not use alcohol, tobacco, or illicit drugs. Physical examination is within normal limits. Which of the following changes in this patient's acid-base physiology is most likely to be seen?

	Arterial pH	Renal H^+ secretion	Renal HCO_3^- reabsorption
A.	↓	↑	↓
B.	↑	↓	↓
C.	↑	No change	↓
D.	No change	↓	↓
E.	↓	↓	↑
F.	↑	↑	No change

Submit

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	Arterial pH	Renal H^+ secretion	Renal HCO_3^- reabsorption
A. (7%)	↓	↑	↓
✓ B. (54%)	↑	↓	↓
C. (16%)	↑	No change	↓
D. (1%)	No change	↓	↓
E. (10%)	↓	↓	↑
F. (9%)	↑	↑	No change

Omitted
Correct answer
B

54%
Answered correctly

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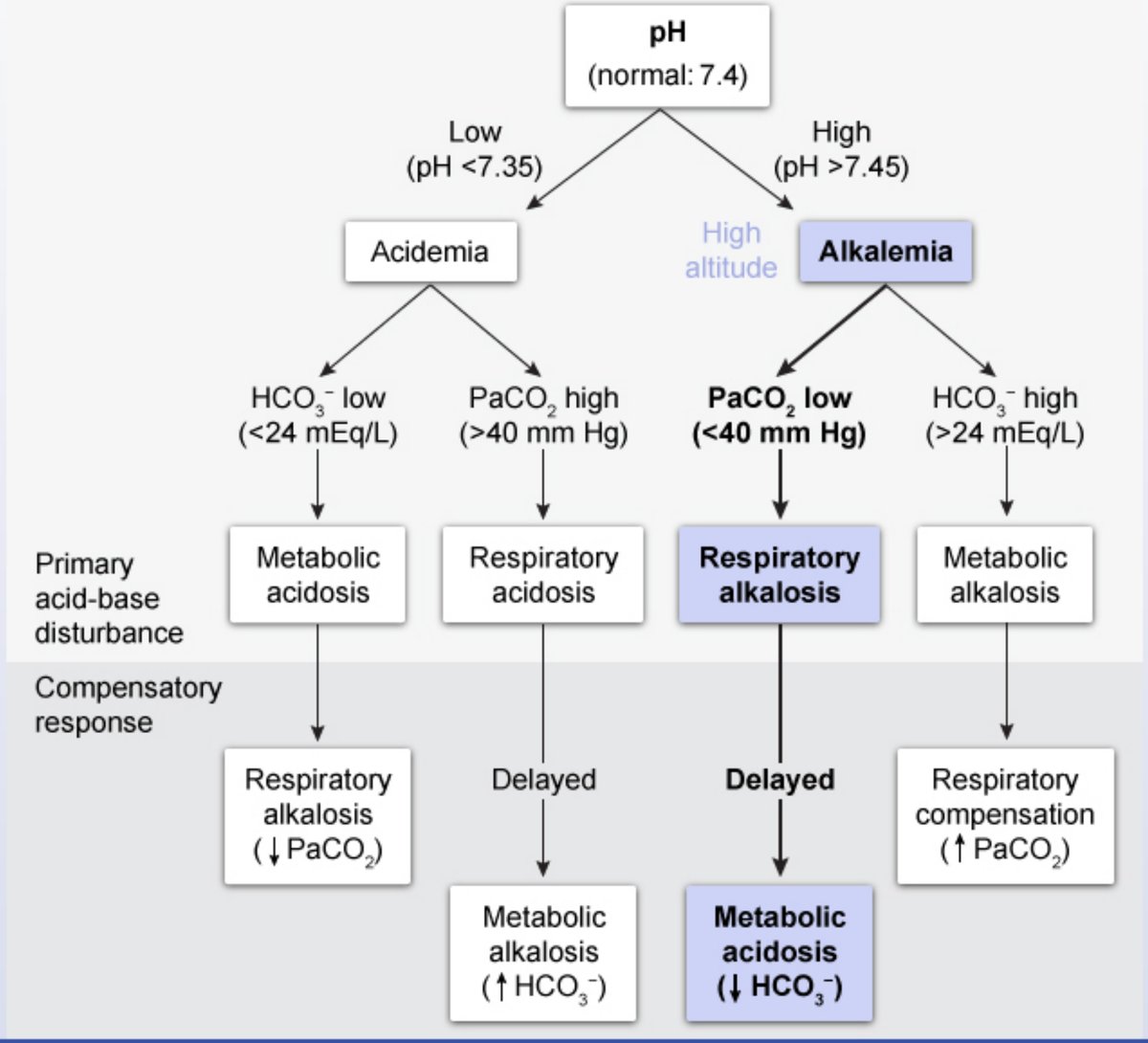
Arterial blood gas interpretation of acid-base disorders



HCO_3^- = bicarbonate; $PaCO_2$ = partial pressure of carbon dioxide in arterial blood.

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At **high altitude**, the low barometric pressure decreases the partial pressure of inspired oxygen (PiO_2) and leads to **hypoxemia**, which in turn triggers a chemoreceptor-mediated increase in respiratory drive with resulting **hyperventilation**. An unwanted effect of the hyperventilation is excessive expiration of CO_2, leading to **respiratory alkalosis** and increased blood pH. The hypoxemia and alkalemia can cause **altitude sickness**, which presents with headache, fatigue, lightheadedness, nausea, and insomnia.

Over time, the body makes physiologic adjustments to better tolerate high altitude:

- In response to respiratory alkalosis, the **kidneys decrease HCO_3^- reabsorption** and **H^+ secretion** to create a **compensatory metabolic acidosis** (a process that **begins within hours** and requires several days to complete).
- Alkalosis also causes a left shift in the hemoglobin dissociation curve, which initially impairs tissue oxygen delivery; however, the curve is shifted back to the right by increased production of 2,3-biphosphoglycerate in red blood cells, facilitating O_2 unloading.
- Chronic hypoxemia triggers increased erythropoietin secretion by the kidneys with a resulting increase in red blood cell production (a process that requires several weeks).

On initial exposure to high altitude, the administration of a carbonic anhydrase inhibitor (eg, **acetazolamide**) can accelerate the decrease in HCO_3^- reabsorption by the kidneys to help relieve the alkalemia and treat altitude sickness.

Educational objective:
At high altitude, the low partial pressure of inspired oxygen (PiO_2) leads to hypoxemia with consequent hyperventilation and respiratory alkalosis. The hypoxemia and alkalemia can cause symptoms of altitude sickness (eg, headache, fatigue, lightheadedness). The kidneys respond by creating a compensatory metabolic acidosis and by increasing erythropoietin secretion.

References

- Physiology in medicine: a physiologic approach to prevention and treatment of acute high-altitude illnesses.
- High-altitude headache and acute mountain sickness.

HCO_3^- = bicarbonate; $PaCO_2$ = partial pressure of carbon dioxide in arterial blood.

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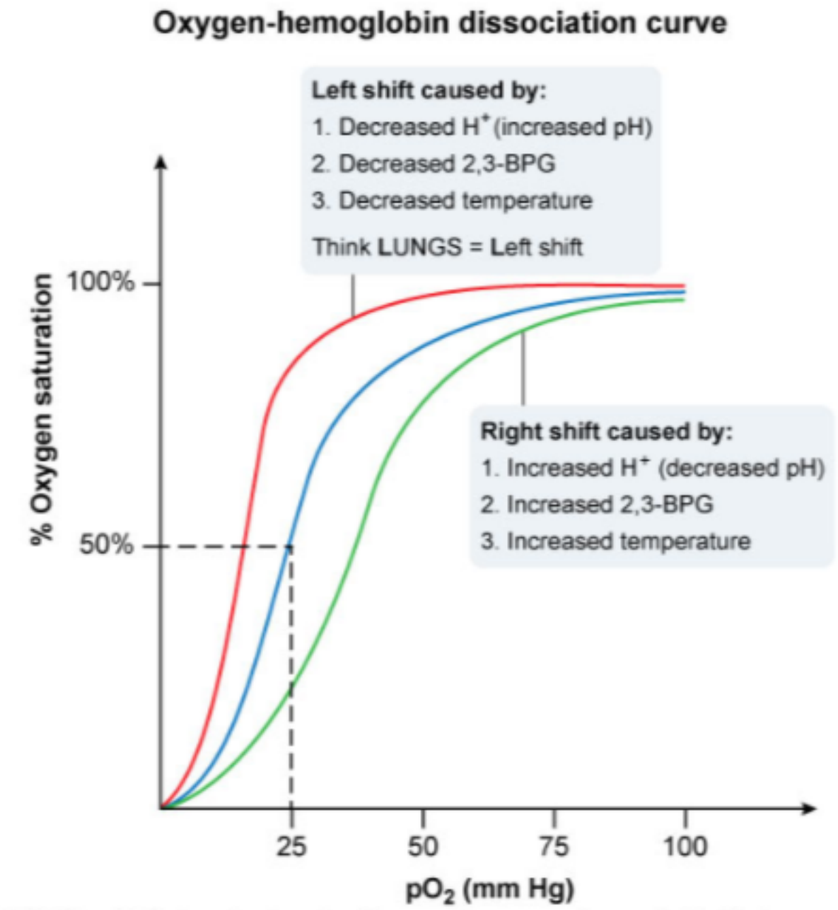

2,3-BPG = 2,3-bisphosphoglycerate; pO_2 = partial pressure of oxygen in the blood.

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References

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- High-altitude headache and acute mountain sickness.

Physiology	Renal, Urinary Systems & Electrolytes	High altitude illness
Subject	System	Topic

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A 43-year-old woman with borderline personality disorder is brought to the emergency department after taking an undetermined number of pills. She is lethargic but arousable. She refuses to answer questions. Blood pressure is 110/60 mm Hg and heart rate is 120/min and regular. Laboratory results are as follows:

Serum chemistry	
Sodium	139 mEq/L
Potassium	3.3 mEq/L
Chloride	98 mEq/L
Bicarbonate	13 mEq/L
Arterial blood gases on room air	
pH	7.46
$PaCO_2$	19 mm Hg
PaO_2	96 mm Hg
Oxygen saturation	99%

Which of the following best describes this patient's acid-base disturbance?

A. Metabolic acidosis and metabolic alkalosis
B. Metabolic acidosis and respiratory acidosis
C. Metabolic acidosis and respiratory alkalosis
D. Metabolic alkalosis and respiratory acidosis
E. Metabolic alkalosis and respiratory alkalosis

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Serum chemistry

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Chloride	98 mEq/L
Bicarbonate	13 mEq/L

Arterial blood gases on room air

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PaO_2	96 mm Hg
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C. Metabolic acidosis and respiratory alkalosis
D. Metabolic alkalosis and respiratory acidosis
E. Metabolic alkalosis and respiratory alkalosis

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Serum chemistry

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Bicarbonate	13 mEq/L

Arterial blood gases on room air

pH	7.46
$PaCO_2$	19 mm Hg
PaO_2	96 mm Hg
Oxygen saturation	99%

Which of the following best describes this patient's acid-base disturbance?

A. Metabolic acidosis and metabolic alkalosis (0%)
B. Metabolic acidosis and respiratory acidosis (1%)
✓ C. Metabolic acidosis and respiratory alkalosis (83%)
D. Metabolic alkalosis and respiratory acidosis (4%)
E. Metabolic alkalosis and respiratory alkalosis (9%)

Omitted
Correct answer

83%
Answered correctly

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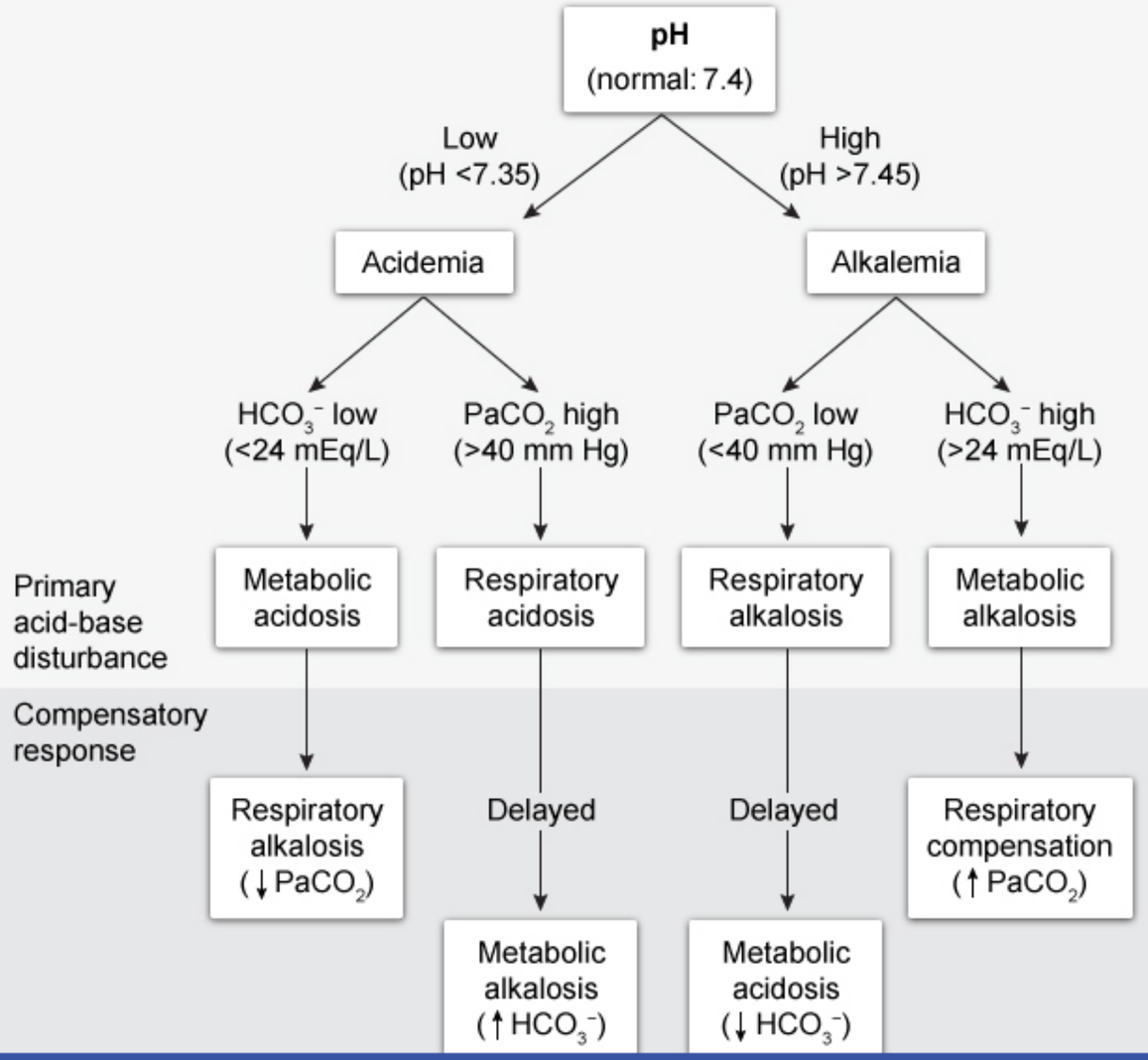
Arterial blood gas interpretation of acid-base disorders



This patient's elevated pH and low $PaCO_2$ (<40 mm Hg) are suggestive of **primary respiratory alkalosis**. Normally, serum bicarbonate is expected to drop in response. However, a bicarbonate of 13 mEq/L is much lower than the expected secondary compensation, which indicates a second primary acid-base disorder. The lower-than-expected serum bicarbonate with a high anion gap [139 − (98 + 13) = 28] is consistent with a concomitant **primary anion gap metabolic acidosis**. This mixed respiratory alkalosis and anion gap metabolic acidosis is most likely the result of **salicylate poisoning**:

- Primary respiratory alkalosis is due to direct stimulation of the medullary respiratory center by excess salicylate, resulting in both an **increased respiratory rate** and **tidal volume** (ie, increased minute ventilation).
- Primary metabolic acidosis occurs mostly because salicylate uncouples oxidative phosphorylation, which results in **increased production of lactic acid** and ketoacids in peripheral tissues. Excess salicylic acid in the serum also makes a minor contribution. The ionized form of these compounds also increases the anion gap (unmeasured anions).

The pH is typically near or within normal range in patients with salicylate poisoning because of the opposing influences of the respiratory alkalosis and metabolic acidosis.

(Choice A) Primary metabolic acidosis and primary metabolic alkalosis can simultaneously develop in the setting of 2 disparate pathologic processes (eg, renal failure and vomiting). The pH and bicarbonate levels can be increased, normal, or decreased, depending on the severity of the metabolic acidosis compared with the metabolic alkalosis.

(Choice B) Primary metabolic acidosis with primary respiratory acidosis (eg, sepsis and hypoventilatory respiratory failure) typically leads to significant acidemia (very low pH) with low bicarbonate and high $PaCO_2$.

(Choice D) Primary metabolic alkalosis with primary respiratory acidosis (eg, vomiting and hypoventilation due to opioid overdose) is expected to show elevated bicarbonate and $PaCO_2$; the pH can reflect alkalemia or acidemia, depending on the relative severity of the 2 disturbances.

(Choice E) Primary metabolic alkalosis with primary respiratory alkalosis (eg, vomiting and hyperventilation due to anxiety) is expected to cause significant alkalemia (very high pH) with high bicarbonate and low $PaCO_2$.

Educational objective:
Salicylate poisoning causes mixed primary respiratory alkalosis and primary anion gap metabolic acidosis. Mixed acid-base disturbances can be recognized by inappropriate secondary compensation for one of the primary disturbances, indicating that an additional primary disturbance must

of **salicylate poisoning**:

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Educational objective:
Salicylate poisoning causes mixed primary respiratory alkalosis and primary anion gap metabolic acidosis. Mixed acid-base disturbances can be recognized by inappropriate secondary compensation for one of the primary disturbances, indicating that an additional primary disturbance must be present.

Physiology	Renal, Urinary Systems & Electrolytes	Salicylate poisoning
Subject	System	Topic

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alkalosis (↓ $PaCO_2$)

compensation (↑ $PaCO_2$)

This patient's elevated pH
expected to drop in respo
second primary acid-base
concomitant **primary anio**
of **salicylate poisoning**:

- Primary respiratory
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- Primary metabolic a
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(Choice B) Primary metabolic acidosis with primary respiratory acidosis (eg, sepsis and hypoventilatory respiratory failure) typically leads to significant acidemia (very low pH) with low bicarbonate and high $PaCO_2$.

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Appropriate compensatory $PaCO_2$ or bicarbonate changes in acid-base disorders

Metabolic acidosis (acute or chronic)	Expected $PaCO_2$ = (1.5 × bicarbonate) + 8 ± 2 (Winters formula)
Metabolic alkalosis (acute or chronic)	~7 mm Hg ↑ in $PaCO_2$ per 10 mEq/L ↑ in bicarbonate
Respiratory acidosis (chronic only*)	~4 mEq/L ↑ in bicarbonate per 10 mm Hg ↑ in $PaCO_2$
Respiratory alkalosis (chronic only*)	~4 mEq/L ↓ in bicarbonate per 10 mm Hg ↓ in $PaCO_2$

*Compensation for respiratory disturbances is minimal in the acute setting. The full level of chronic compensation is achieved after ~72 hr. For simplicity, normal baseline $PaCO_2$ and bicarbonate should be considered 40 mm Hg and 24 mEq/L, respectively.

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alkalosis ($\downarrow PaCO_2$)

compensation ($\uparrow PaCO_2$)

This patient's elevated pH
expected to drop in respo
second primary acid-base
concomitant **primary anio**
of **salicylate poisoning**:

- Primary respiratory
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processes (eg, renal failur
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(Choice B) Primary metabolic acidosis with primary respiratory acidosis (eg, sepsis and hypoventilatory respiratory failure) typically leads to significant acidemia (very low pH) with low bicarbonate and high $PaCO_2$.

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Anion gap metabolic acidosis	
Calculation	Anion gap = sodium – (chloride + bicarbonate) (Normal: 10-14)
Common causes Mnemonic: MUDPILES	• Methanol • Uremia • Diabetic ketoacidosis • Propylene glycol/paraldehyde • Isoniazid/iron • Lactic acidosis • Ethylene glycol (antifreeze) • Salicylates (aspirin)

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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31

Physiologists are studying how the plasma concentration of various substances affects the degree to which they are excreted in the urine. During one experiment, a substance freely filtered at the glomerulus is infused intravenously at various rates. The plasma concentration (mg/mL) and urinary excretion rate (mg/min) of the substance are monitored. Assuming a constant glomerular filtration rate (GFR) of 100 mL/min, the following observations are made:

	Preinfusion	Low-dose infusion	Medium-dose infusion	High-dose infusion
Filtered load (mg/min) (GFR × plasma concentration)	100	200	400	600
Urinary excretion rate (mg/min)	0	100	300	500

Which of the following substances is most likely to demonstrate a similar pattern of filtration and excretion in a healthy adult?

A. Albumin
B. Creatinine
C. Glucose
D. Mannitol
E. Urea

Submit

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Physiologists are studying how the plasma concentration of various substances affects the degree to which they are excreted in the urine. During one experiment, a substance freely filtered at the glomerulus is infused intravenously at various rates. The plasma concentration (mg/mL) and urinary excretion rate (mg/min) of the substance are monitored. Assuming a constant glomerular filtration rate (GFR) of 100 mL/min, the following observations are made:

	Preinfusion	Low-dose infusion	Medium-dose infusion	High-dose infusion
Filtered load (mg/min) (GFR × plasma concentration)	100	200	400	600
Urinary excretion rate (mg/min)	0	100	300	500

Which of the following substances is most likely to demonstrate a similar pattern of filtration and excretion in a healthy adult?

A. Albumin (1%)
B. Creatinine (26%)
C. Glucose (43%)
D. Mannitol (8%)
E. Urea (19%)

Omitted
Correct answer
C

43%
Answered correctly

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04/27/2020
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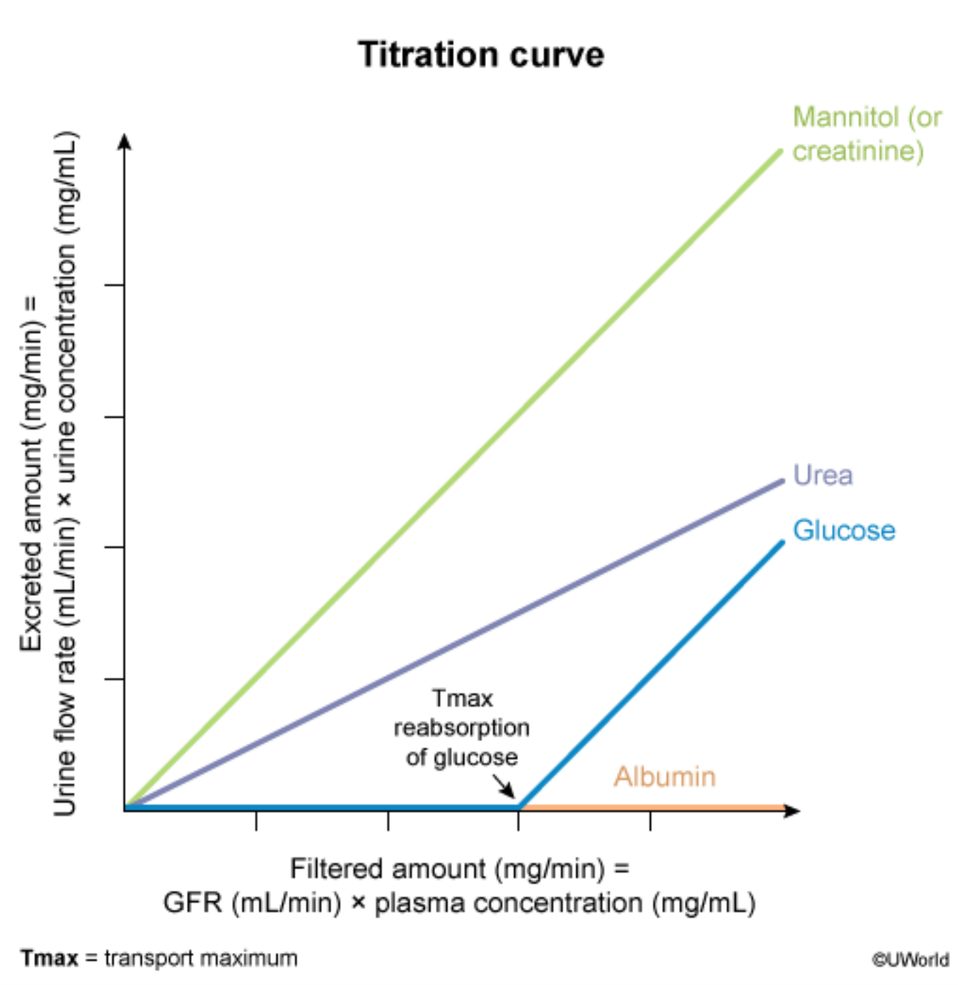
Explanation



At physiologic levels (preinfusion), the experimental substance is filtered at the glomerulus but completely reabsorbed, and no amount is excreted in the urine. However, as the concentration and filtered load are increased, the substance begins to spill into the urine, suggesting a **limit to the rate** at which it can be **reabsorbed**. This rate, called the **transport maximum** (Tmax) of a substance, is determined by the capacity of transporters available for active reabsorption.

Tmax = transport maximum ©UWorld

At physiologic levels (preinfusion), the experimental substance is filtered at the glomerulus but completely reabsorbed, and no amount is excreted in the urine. However, as the concentration and filtered load are increased, the substance begins to spill into the urine, suggesting a **limit to the rate** at which it can be **reabsorbed**. This rate, called the **transport maximum** (Tmax) of a substance, is determined by the capacity of transporters available for active reabsorption.

The reabsorption pattern is **similar** to that of **glucose**, which is **filtered in the glomerulus** and **reabsorbed completely** in the proximal tubule under normal serum concentrations. However, once glucose reaches its Tmax, the excess filtered load passes unabsorbed through the tubules. The serum concentration at which glucosuria begins, called the threshold of glucose, is approximately **200 mg/dL**.

(Choice A) Albumin is a large, polarized plasma protein that is not filtered in a normal, healthy glomerulus, so urinary excretion would remain at 0 mg/min.

(Choices B and D) Creatinine and mannitol (an osmotic diuretic) are freely filtered in the glomerulus and are not reabsorbed. As a result, the urinary excretion of these substances is dependent on the glomerular filtration rate and remains equal to the filtered load of the substance regardless of the serum concentration (note that urinary excretion of creatinine is slightly more than the filtered rate due to tubular secretion).

(Choice E) Urea is filtered and then reabsorbed by passive diffusion into the peritubular capillaries. Approximately 20%-50% of the filtered load is normally reabsorbed. Urea has no Tmax because it is passively reabsorbed.

Educational objective:
At normal plasma concentrations of glucose, the renal tubules reabsorb the entire filtered load of glucose because it is below the maximum tubular reabsorption ability (transport maximum of glucose). At higher plasma concentrations, glucose is excreted when the filtered amount exceeds the transport maximum. The serum concentration at which glucosuria begins, called the threshold of glucose, is approximately 200 mg/dL.

Physiology	Renal, Urinary Systems & Electrolytes	GFR
Subject	System	Topic

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A 58-year-old man comes to the emergency department due to generalized weakness, anorexia, and nausea for the past several weeks. He also reports lower extremity swelling but has had no dyspnea or chest pain. The patient was diagnosed with hypertension several years ago but did not follow up and takes no medications. Blood pressure is 182/100 mm Hg and pulse is 84/min. Physical examination shows pitting edema of the bilateral lower extremities. Laboratory studies reveal elevated serum creatinine and blood urea nitrogen levels. During evaluation of renal dysfunction, total urinary creatinine is measured over a 24-hour period, and creatinine clearance is calculated using the serum and urine creatinine concentrations and urinary volume. Compared to the calculated creatinine clearance, this patient's true glomerular filtration rate is most likely to be:

- A. 20% higher
- B. 20% lower
- C. 90% higher
- D. 90% lower
- E. Equal

Submit

A 58-year-old man comes to the emergency department due to generalized weakness, anorexia, and nausea for the past several weeks. He also reports lower extremity swelling but has had no dyspnea or chest pain. The patient was diagnosed with hypertension several years ago but did not follow up and takes no medications. Blood pressure is 182/100 mm Hg and pulse is 84/min. Physical examination shows pitting edema of the bilateral lower extremities. Laboratory studies reveal elevated serum creatinine and blood urea nitrogen levels. During evaluation of renal dysfunction, total urinary creatinine is measured over a 24-hour period, and creatinine clearance is calculated using the serum and urine creatinine concentrations and urinary volume. Compared to the calculated creatinine clearance, this patient's true glomerular filtration rate is most likely to be:

- A. 20% higher (19%)
- ✓ B. 20% lower (65%)
- C. 90% higher (1%)
- D. 90% lower (4%)
- E. Equal (10%)

Omitted
Correct answer
B

65%
Answered correctly

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04/04/2020
Last Updated

Explanation

This patient with elevated creatinine and blood urea nitrogen levels has symptoms of uremia (eg, weakness, nausea, anorexia) due to kidney disease, most likely from chronic uncontrolled hypertension.

Kidney filtration function is reflected by the **glomerular filtration rate (GFR)**, which is the sum of the filtration rates of all the nephrons in the

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This patient with elevated creatinine and blood urea nitrogen levels has symptoms of uremia (eg, weakness, nausea, anorexia) due to kidney disease, most likely from chronic uncontrolled hypertension.

Kidney filtration function is reflected by the **glomerular filtration rate (GFR)**, which is the sum of the filtration rates of all the nephrons in the kidneys. Normal GFR ranges between 120 and 130 mL/min per 1.73 m^2 of body surface area, and can vary considerably based on age, sex, and body habitus. GFR is reduced in both chronic kidney disease (due to loss of functional nephrons) and acute kidney injury (eg, due to decreased renal perfusion).

The GFR can be directly measured using an **ideal filtration marker** that is **freely filtered** across the glomerulus and is **not metabolized, secreted, or reabsorbed** by the kidney tubules. However, this is time intensive and invasive and requires multiple blood draws. In addition, the substance previously used to perform these calculations, inulin, is no longer available in the United States.

Because of the limitations in directly measuring GFR, renal filtration function is more commonly estimated using **creatinine**, a waste product generated from the breakdown of creatine in the muscles. Creatinine is released from muscle at a relatively constant rate and is neither metabolized nor reabsorbed by the kidney. However, in addition to passive filtration, a portion of creatinine is **actively secreted** by the proximal tubules. Therefore, uncorrected creatinine clearance **overestimates the GFR by approximately 10%-20%**. Creatinine clearance has further limitations in patients with low muscle mass (eg, malnutrition, lower extremity amputation) or high- or low-protein diets.

(Choices A, C, D, and E) Creatinine clearance overestimates the GFR by 10%-20% due to the proximal tubular secretion of creatinine.

Educational objective:
Glomerular filtration rate (GFR) can be assessed using an ideal filtration marker that is freely filtered across the glomerulus and is not metabolized, secreted, or reabsorbed by the kidney tubules. In common practice, GFR is estimated using creatinine clearance. However, creatinine is actively secreted by the proximal tubules, so uncorrected creatinine clearance overestimates the GFR by approximately 10%-20%.

Physiology	Renal, Urinary Systems & Electrolytes	Creatinine clearance
Subject	System	Topic

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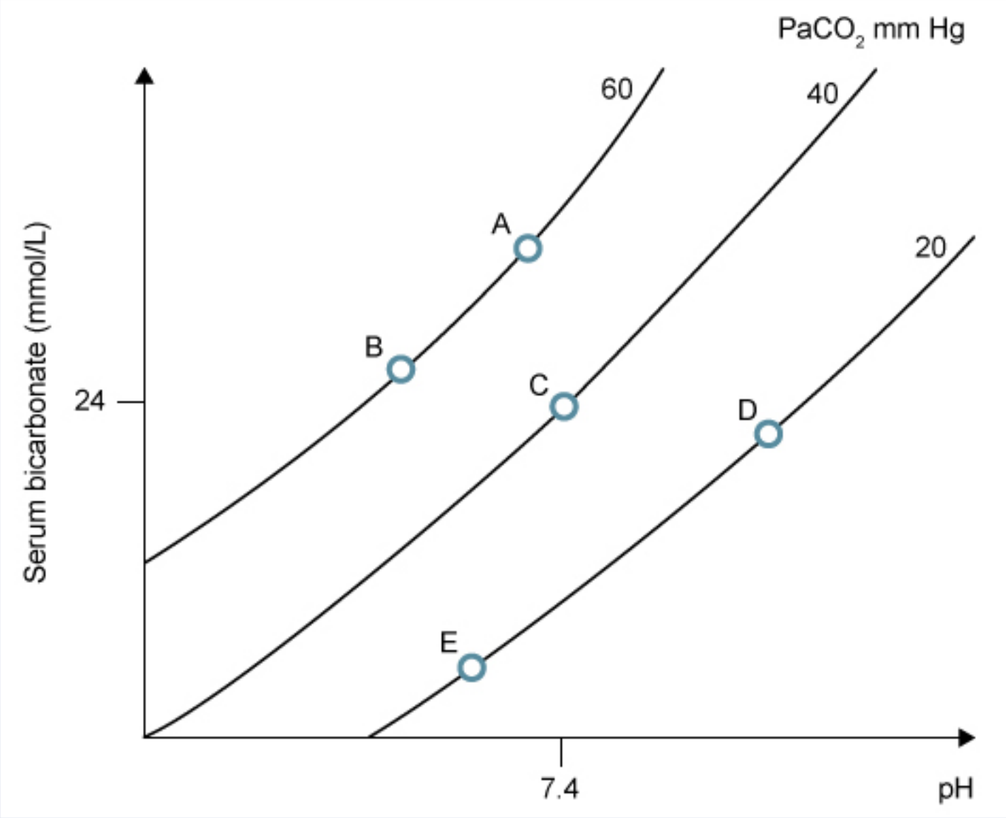
A 23-year-old man comes to the emergency department due to abdominal pain and nausea for the last few hours. He also reports an episode of vomiting and has noticed that his urine has a fruity odor. The patient has had increased thirst and urination for the past several days along with weight loss. He has no known medical problems and takes no medications. Physical examination reveals pallor with cool extremities. The abdomen is soft, without tenderness to palpation. Laboratory studies are ordered to confirm the diagnosis. Which of the following points on the graph below best corresponds to this patient's acid-base status?

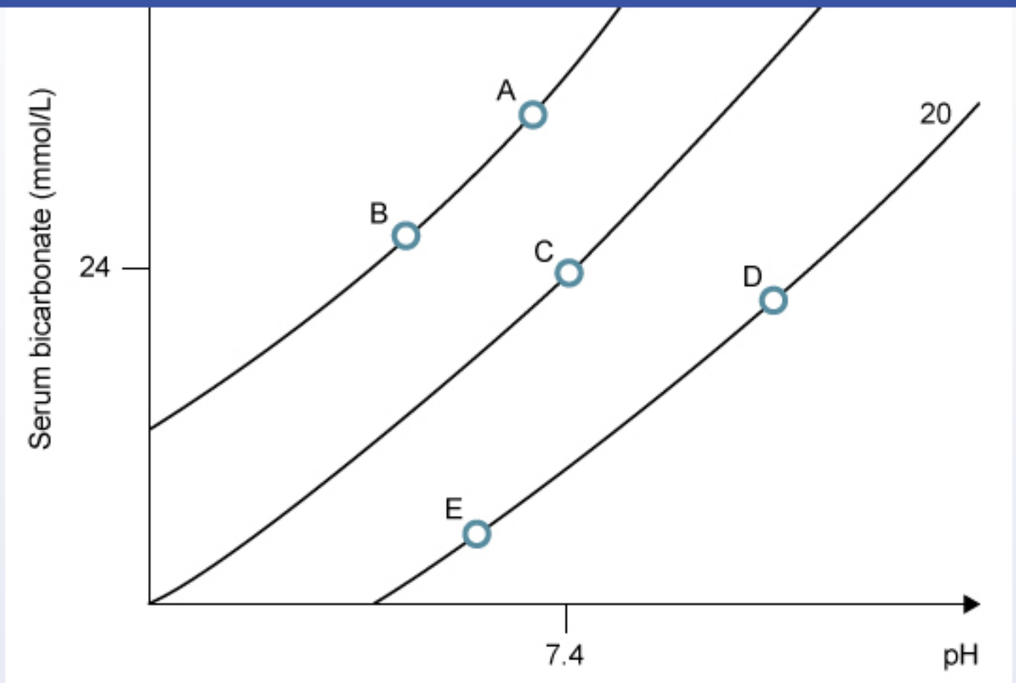
A. Point A
B. Point B
C. Point C
D. Point D
E. Point E

Submit

A 23-year-old man comes to the emergency department due to abdominal pain and nausea for the last few hours. He also reports an episode of vomiting and has noticed that his urine has a fruity odor. The patient has had increased thirst and urination for the past several days along with weight loss. He has no known medical problems and takes no medications. Physical examination reveals pallor with cool extremities. The abdomen is soft, without tenderness to palpation. Laboratory studies are ordered to confirm the diagnosis. Which of the following points on the graph below best corresponds to this patient's acid-base status?



A. Point A



A. Point A
B. Point B
C. Point C
D. Point D
E. Point E

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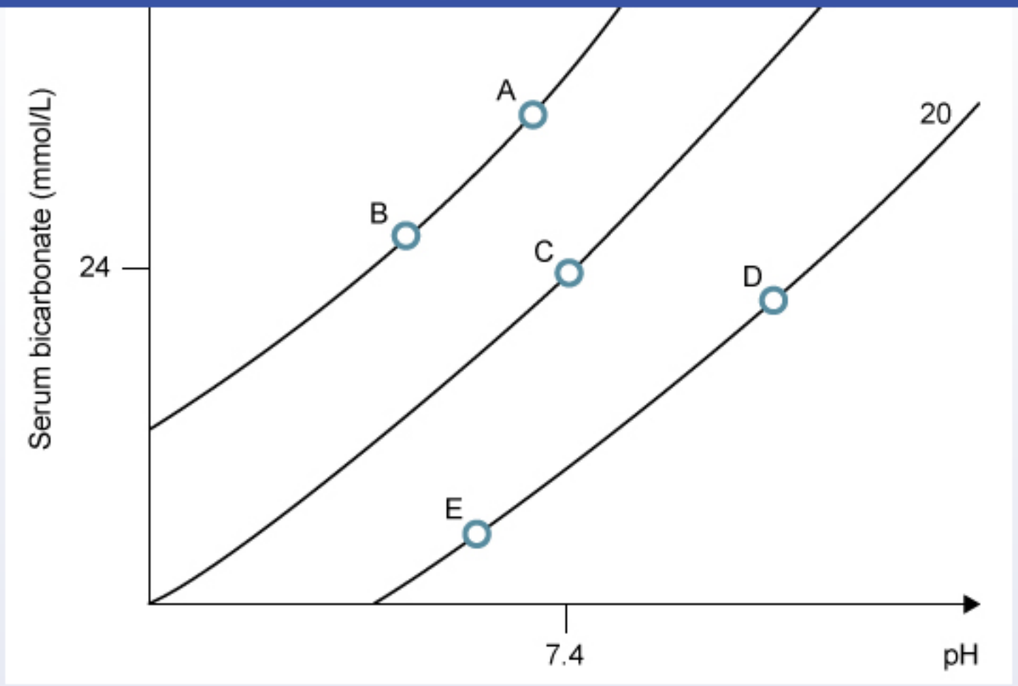

A. Point A (3%)

B. Point B (12%)

C. Point C (3%)

D. Point D (5%)

✓ E. Point E (75%)

Omitted
Correct answer

75%
Answered correctly

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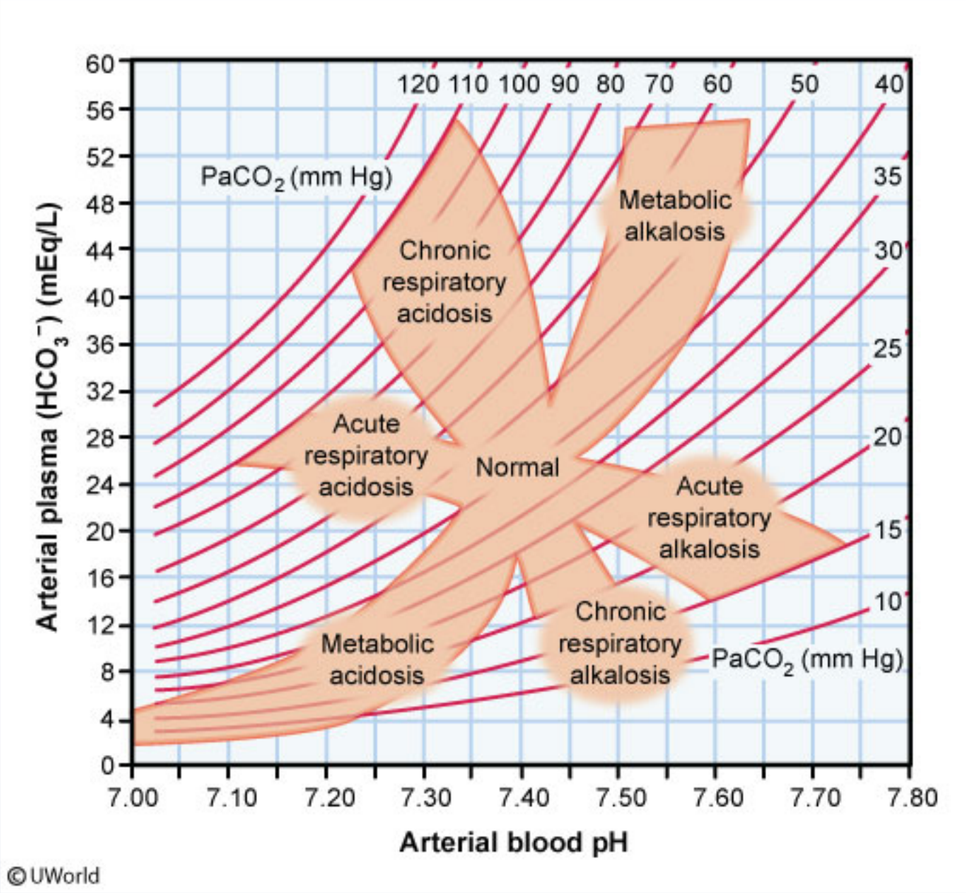
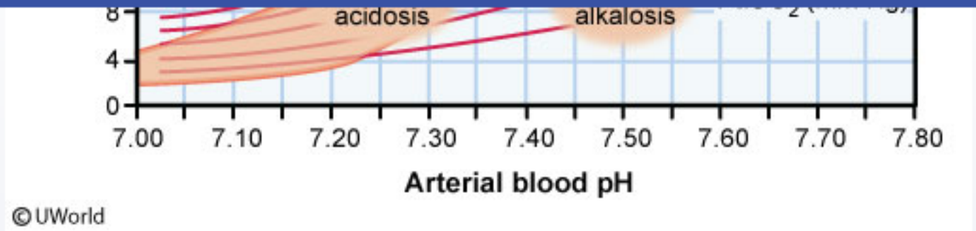


Diabetic ketoacidosis (DKA) is characterized by polydipsia, polyuria, and a fruity odor to the breath and/or urine. Patients frequently present with abdominal pain, nausea, and vomiting (as seen in this patient). Laboratory results reveal **elevated anion gap metabolic acidosis** secondary to accumulation of **ketone bodies** (eg, beta-hydroxybutyrate and acetoacetate); excreted acetone causes the fruity smell associated with DKA. Serum bicarbonate is used to buffer the excess ketoacids in the blood, so the **bicarbonate level falls**. Metabolic acidosis also stimulates ventilation by a chemoreceptor reflex that causes **compensatory respiratory alkalosis**, which lowers CO_2 partial pressure.



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The normal acid-base balance in a healthy individual is represented in the graph above by Point C **(Choice C)**. An individual with DKA will have low blood pH, low serum HCO_3^-, and low $PaCO_2$ (Point E).

(Choices A and B) Point B corresponds to a primary respiratory acidosis (low pH and high $PaCO_2$). Point A reflects chronic respiratory acidosis with compensatory metabolic alkalosis (renal retention of bicarbonate).

(Choice D) Point D corresponds to a primary respiratory alkalosis as seen in hyperventilatory states (eg, pulmonary embolism, anxiety, high altitude).

Educational objective:
Diabetic ketoacidosis (DKA) is characterized by polydipsia, polyuria, and a fruity odor to the breath and/or urine. DKA is associated with elevated anion gap metabolic acidosis that is usually accompanied by compensatory respiratory alkalosis. This combination yields a low pH, low serum bicarbonate, and low $PaCO_2$.

Physiology	Renal, Urinary Systems & Electrolytes	Diabetic ketoacidosis
Subject	System	Topic

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A 34-year-old woman comes to the office due to a 3-day history of watery diarrhea. The patient has no fever. She has no other medical conditions and takes no medications. Blood pressure is 120/80 mm Hg and pulse is 90/min. Examination shows mild abdominal discomfort but is otherwise normal. Compared to normal laboratory values, which of the following findings are most likely present in this patient?

	Blood pH	$PaCO_2$	Serum bicarbonate
A.	Low	Low	Low
B.	Low	High	Normal
C.	Low	High	High
D.	High	Low	Low
E.	High	High	High

Submit

A 34-year-old woman comes to the office due to a 3-day history of watery diarrhea. The patient has no fever. She has no other medical conditions and takes no medications. Blood pressure is 120/80 mm Hg and pulse is 90/min. Examination shows mild abdominal discomfort but is otherwise normal. Compared to normal laboratory values, which of the following findings are most likely present in this patient?

	Blood pH	$PaCO_2$	Serum bicarbonate
✓ A. (74%)	Low	Low	Low
B. (3%)	Low	High	Normal
C. (2%)	Low	High	High
D. (7%)	High	Low	Low
E. (11%)	High	High	High

Omitted
Correct answer
A

74%
Answered correctly

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05/28/2020
Last Updated

Explanation

Common causes of primary acid-base disturbance	
Metabolic acidosis	**Elevated anion gap** • Poor tissue perfusion (ie, lactic acidosis) • Diabetic ketoacidosis • Renal failure (ie, uremia) • Certain toxicities (eg, methanol, ethylene glycol) **Normal anion gap** • Severe diarrhea • Renal tubular acidosis • Excess normal saline infusion
Metabolic alkalosis	• Nasogastric suctioning or severe vomiting • Diuretic overuse • Primary hyperaldosteronism
Respiratory acidosis (hypoventilation)	• Central respiratory depression (eg, opioid overdose) • OHS, neuromuscular weakness • Chronic obstructive pulmonary disease
Respiratory alkalosis (hyperventilation)	• Acute V/Q mismatch (eg, PE, pneumonia) • Anxiety, inadequate pain control • High altitude, pregnancy

OHS = obesity hypoventilation syndrome; PE = pulmonary embolism; V/Q = ventilation/perfusion.

This patient with several days of **diarrhea** is expected to have **primary metabolic acidosis**, with low blood pH (<7.35), low serum bicarbonate (HCO_3^-) (<24 mEq/L), and compensatory low partial pressure of carbon dioxide in arterial blood ($PaCO_2$) (<40 mm Hg). Severe diarrhea involves substantial **loss of HCO_3^-** in the stool, leading to nonanion gap metabolic acidosis. The **reduced blood pH** increases ventilatory drive to facilitate

Respiratory alkalosis (hyperventilation)	• Acute V/Q mismatch (eg, PE, pneumonia) • Anxiety, inadequate pain control • High altitude, pregnancy

OHS = obesity hypoventilation syndrome; PE = pulmonary embolism; V/Q = ventilation/perfusion.

This patient with several days of **diarrhea** is expected to have **primary metabolic acidosis**, with low blood pH (<7.35), low serum bicarbonate (HCO_3^-) (<24 mEq/L), and compensatory low partial pressure of carbon dioxide in arterial blood ($PaCO_2$) (<40 mm Hg). Severe diarrhea involves substantial **loss of HCO_3^-** in the stool, leading to nonanion gap metabolic acidosis. The **reduced blood pH** increases ventilatory drive to facilitate **CO_2 removal** by the lungs, creating a **compensatory respiratory alkalosis**.

(Choices B and C) Low pH with high $PaCO_2$ is consistent with respiratory acidosis. Full metabolic compensation via HCO_3^- reabsorption by the kidneys requires approximately 72 hours; therefore, HCO_3^- is high in chronic respiratory acidosis (eg, CO_2 retention due to chronic obstructive pulmonary disease) and near normal in acute respiratory acidosis (eg, suppressed respiratory drive due to opioid overdose).

(Choice D) High pH with low $PaCO_2$ represents respiratory alkalosis, as occurs with hyperventilation at high altitude. HCO_3^- is low due to compensatory metabolic acidosis.

(Choice E) High pH with high HCO_3^- represents metabolic alkalosis, as occurs with the loss of H^+ with severe vomiting. $PaCO_2$ is high due to compensatory respiratory acidosis.

Educational objective:
Severe diarrhea causes substantial loss of bicarbonate (HCO_3^-) in the stool and is a common cause of nonanion gap metabolic acidosis. Low blood pH (<7.35) and low serum HCO_3^- (<24 mEq/L) are expected with compensatory low arterial partial pressure of carbon dioxide ($PaCO_2$) (compensatory respiratory alkalosis).

Physiology	Renal, Urinary Systems & Electrolytes	Metabolic acidosis
Subject	System	Topic

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- Acute V/Q mismatch (eg, PE, pneumonia)

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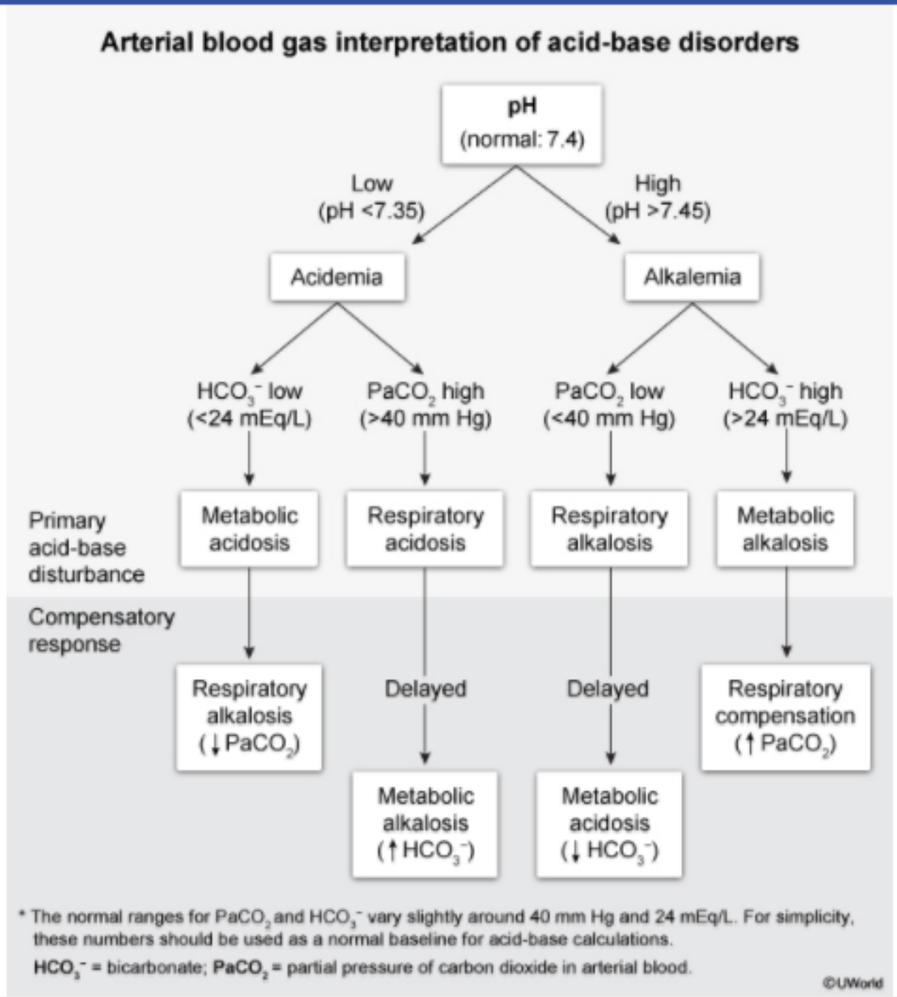

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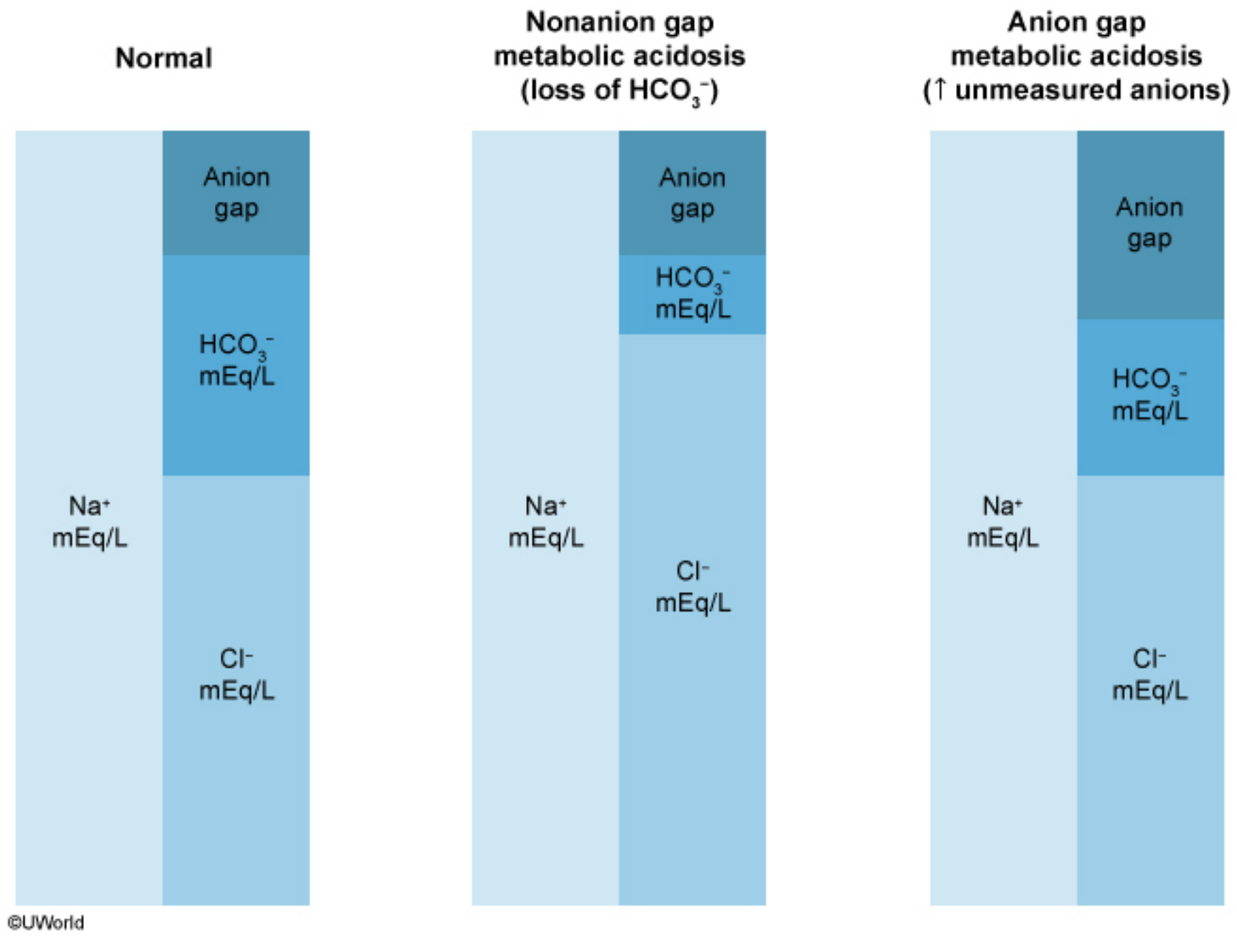

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A longitudinal study is conducted to assess changes in renal function over time in patients with recently diagnosed type 2 diabetes mellitus. An initial set of laboratory tests is obtained in newly enrolled patients to establish baseline renal function parameters. The following measurements are taken from a 42-year-old male volunteer.

	Urine	Serum
Creatinine	110.0 mg/dL	1.1 mg/dL
Glucose	0	80.0 mg/dL
Potassium	50.0 mEq/L	4.0 mEq/L
Uric acid	15.0 mg/dL	3.0 mg/dL
Para-aminohippuric acid	100 mg/mL	0.2 mg/mL

Which of the following is the best estimate of the filtration fraction in this patient assuming a urine flow of 1.0 mL/min?

A. 10%
B. 20%
C. 30%
D. 40%
E. 50%

Submit

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	Urine	Serum
Creatinine	110.0 mg/dL	1.1 mg/dL
Glucose	0	80.0 mg/dL
Potassium	50.0 mEq/L	4.0 mEq/L
Uric acid	15.0 mg/dL	3.0 mg/dL
Para-aminohippuric acid	100 mg/mL	0.2 mg/mL

Which of the following is the best estimate of the filtration fraction in this patient assuming a urine flow of 1.0 mL/min?

A. 10% (18%)
✓ B. 20% (59%)
C. 30% (6%)
D. 40% (5%)
E. 50% (10%)

Omitted
Correct answer
B

59%
Answered correctly

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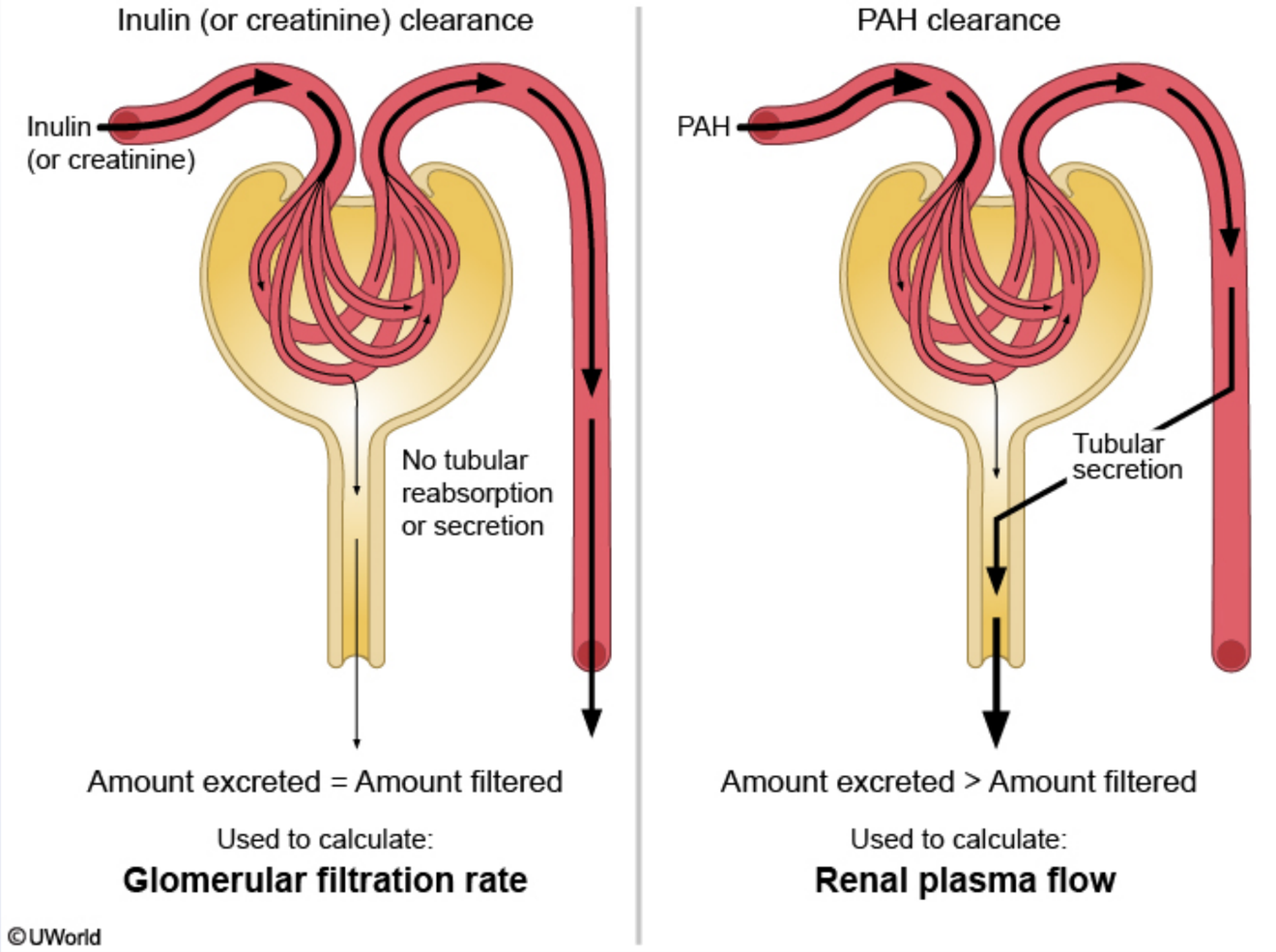

Filtration fraction (FF) is the fraction of plasma flowing through the glomeruli that is filtered across the glomerular capillaries into Bowman's space. It can be thought of as the ratio between the glomerular filtration rate (GFR) and renal plasma flow (RPF):

FF = GFR / RPF

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Filtration fraction (FF) is the fraction of plasma flowing through the glomeruli that is filtered across the glomerular capillaries into Bowman's space. It can be thought of as the ratio between the glomerular filtration rate (GFR) and renal plasma flow (RPF):

FF = GFR / RPF

GFR can be calculated using the inulin or creatinine clearance, as these substances are freely filtered at the glomerulus and have relatively insignificant tubular reabsorption or secretion. RPF can be determined using the para-aminohippuric acid (PAH) clearance as almost all the PAH entering the kidneys is excreted in the urine (mostly via tubular secretion).

The clearance (C) of any given substance S can be calculated as:

C_s = ([Urine concentration of S] x [Urine flow rate]) / (Plasma concentration of S)

In this example, creatinine and PAH clearances can be calculated as:

$C_{Creatinine}$ = (110 mg/dl x 1 ml/min) / 1.1 mg/dl = 100 ml/min

C_{PAH} = (100 mg/ml x 1 ml/min) / 0.2 mg/ml = 500 ml/min

From these values, FF can then be calculated as (100 ml/min) / (500 ml/min) = 0.2 or 20%, which is the typical filtration fraction for a healthy individual.

Educational objective:
The glomerular filtration rate (GFR) can be estimated by the inulin or creatinine clearance, while the renal plasma flow (RPF) is calculated using the para-aminohippuric acid clearance. The filtration fraction (FF = GFR / RPF) is the fraction of the RPF that is filtered across the glomerular capillaries into Bowman's space. It is usually equal to 20% in healthy individuals.

Physiology	Renal, Urinary Systems & Electrolytes	GFR
Subject	System	Topic

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A 55-year-old man comes to the hospital due to progressive fatigue and weakness. Medical history includes type 2 diabetes mellitus and obesity. Laboratory results are as follows:

Serum chemistry

Sodium	138 mEq/L
Chloride	110 mEq/L
Bicarbonate	18 mEq/L

Which of the following is the most likely diagnosis?

A. Diabetic ketoacidosis
B. Lactic acidosis
C. Obesity hypoventilation
D. Primary hyperaldosteronism
E. Renal tubular acidosis

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A. Diabetic ketoacidosis
B. Lactic acidosis
C. Obesity hypoventilation
D. Primary hyperaldosteronism
E. Renal tubular acidosis

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A 55-year-old man comes to the hospital due to progressive fatigue and weakness. Medical history includes type 2 diabetes mellitus and obesity. Laboratory results are as follows:

Serum chemistry

Sodium	138 mEq/L
Chloride	110 mEq/L
Bicarbonate	18 mEq/L

Which of the following is the most likely diagnosis?

A. Diabetic ketoacidosis (7%)
B. Lactic acidosis (12%)
C. Obesity hypoventilation (17%)
D. Primary hyperaldosteronism (2%)
✓ E. Renal tubular acidosis (59%)

Omitted
Correct answer
E

59%
Answered correctly

31 secs
Time Spent

05/28/2020
Last Updated

Explanation

Metabolic acidosis		
Type	**Normal anion gap**	**Elevated anion gap**
Mechanism	• Loss of bicarbonate	• Accumulation of unmeasured acidic compounds
Common causes	• Severe diarrhea • Renal tubular acidosis • Excessive saline infusion	• Lactic acidosis • Diabetic ketoacidosis • Renal failure (uremia) • Methanol, ethylene glycol • Salicylate toxicity

This patient has low serum bicarbonate (HCO_3^-) (<24 mEq/L), consistent with metabolic acidosis. The anion gap is normal at 10 mEq/L; therefore, the most likely diagnosis is **renal tubular acidosis**, a common cause of **nonanion gap metabolic acidosis** (NAGMA).

NAGMA results from **loss of HCO_3^-** (usually from the kidneys or gastrointestinal tract), leading to a relative increase in H^+. In renal tubular acidosis, there is either impaired proximal tubular HCO_3^- reabsorption (type 2) or impaired distal tubular H^+ secretion (types 1 and 4) leading to net HCO_3^- loss. Severe diarrhea, involving loss of HCO_3^- in the stool, is another common cause of NAGMA.

NAGMA is also referred to as **hyperchloremic acidosis** because the decrease in serum HCO_3^- is compensated for by an increase in serum Cl^- to maintain electronegative balance.

(Choices A and B) Anion gap metabolic acidosis results from the addition of unmeasured acidic compounds to the blood. The compounds donate H^+ to bind up serum HCO_3^-, reducing buffering capacity and causing metabolic acidosis. The remaining anionic component increases the anion gap. Common etiologies of anion gap metabolic acidosis include increased production of ketones (eg, acetoacetate, beta-hydroxybutyrate), which occurs with diabetic ketoacidosis, and increased production of lactic acid, which occurs with reduced organ and tissue perfusion (eg, sepsis).

(Choice C) Hypoventilation causes retention of CO_2 and respiratory acidosis. A compensatory metabolic alkalosis with increased serum HCO_3^-

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(Choice C) Hypoventilation causes retention of CO_2 and respiratory acidosis. A compensatory metabolic alkalosis with increased serum HCO_3^- (>24 mEq/L) is expected.

(Choice D) Primary hyperaldosteronism causes excessive loss of H^+ from the renal tubular collecting duct, leading to metabolic alkalosis with increased serum HCO_3^-.

Educational objective:
Nonanion gap metabolic acidosis (NAGMA) results from the loss of bicarbonate (HCO_3^-) (usually from the kidneys or gastrointestinal tract), leading to a relative increase in H^+. Common causes include renal tubular acidosis and severe diarrhea. NAGMA is also referred to as hyperchloremic acidosis because the decrease in serum HCO_3^- is compensated for by an increase in serum chloride to maintain electronegative balance.

References

- Hyperchloremic acidosis.

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Scientists investigating the specifics of kidney function in humans develop a new technique allowing them to measure the concentration of various compounds along the length of the proximal tubule. During an experiment, they record the concentrations of several endogenous substances in the fluid traversing the proximal tubule. Tubular fluid/plasma ultrafiltrate concentration ratios for the measured substances are shown in the image below:

Which of the following substances are most likely to produce lines 2 and 4, respectively?

A. Bicarbonate, sodium

B. Creatinine, amino acids

C. Creatinine, glucose

D. Potassium, chloride

E. Urea, bicarbonate

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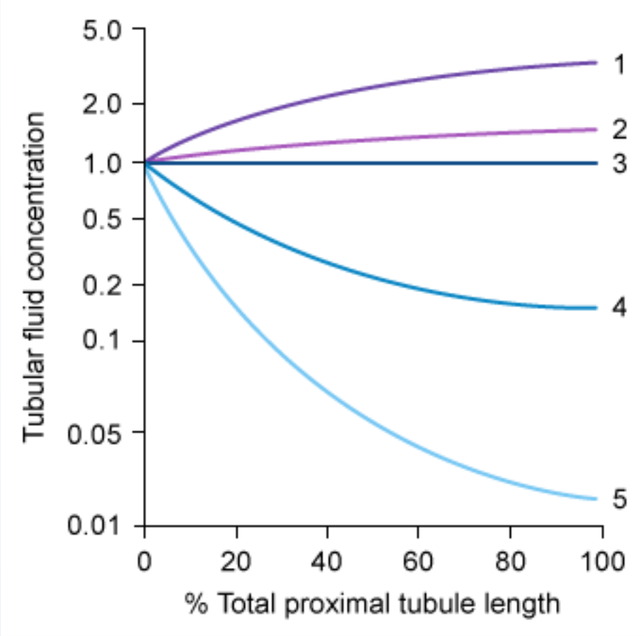

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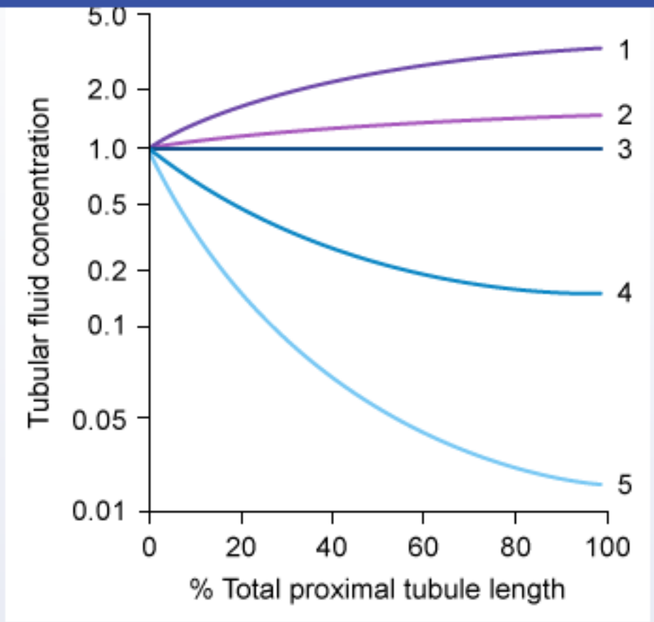
C. Creatinine, glucose

D. Potassium, chloride



Which of the following substances are most likely to produce lines 2 and 4, respectively?

- A. Bicarbonate, sodium
- B. Creatinine, amino acids
- C. Creatinine, glucose
- D. Potassium, chloride
- E. Urea, bicarbonate

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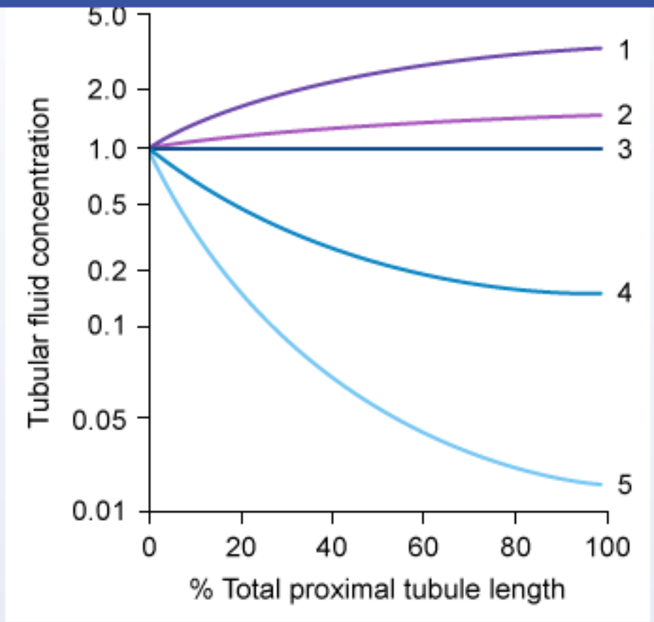

Which of the following substances are most likely to produce lines 2 and 4, respectively?

- A. Bicarbonate, sodium (11%)
- B. Creatinine, amino acids (22%)
- C. Creatinine, glucose (20%)
- D. Potassium, chloride (8%)
- ✓ E. Urea, bicarbonate (36%)

Omitted
Correct answer

36%
Answered correctly

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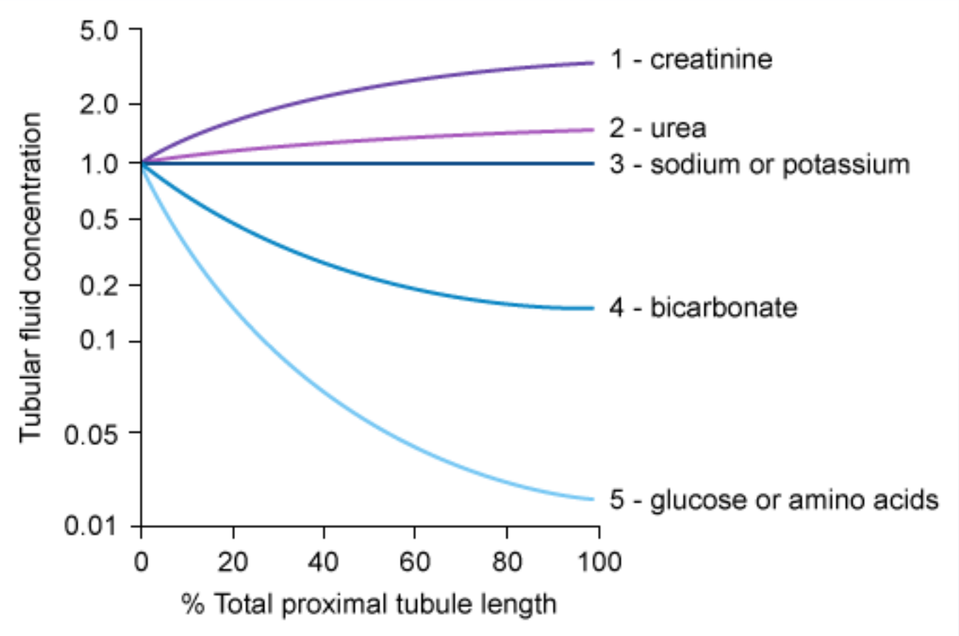
06/11/2020
Last Updated



The tubular fluid/plasma ultrafiltrate value is calculated by dividing the tubular fluid concentration of a given substance in the proximal tubule by the initial concentration of that substance within Bowman's capsule. Therefore, an **upward (positive) slope** indicates an **increasing concentration** of that substance as fluid moves toward distal parts of the tubule, which is usually the result of **secretion or nonreabsorption** of that substance. A **downward slope** indicates **active reabsorption** of that substance in the proximal tubule.

- **Line 1** represents **creatinine**, which is freely filtered in the glomerulus, as well as actively secreted and not reabsorbed along the proximal tubule, resulting in a rapidly increasing concentration in the tubular fluid.
- **Line 2** represents **urea**, which is freely filtered from the glomerular capillaries and is poorly reabsorbed from the proximal tubule, resulting in increasing concentrations along the proximal tubule but less so than with creatinine. Renal handling of urea varies throughout the different tubular systems, but it is ultimately secreted in very high concentrations because it is a waste product of metabolism.
- **Line 3** represents **sodium or potassium**, which is reabsorbed in concentrations approximately equal with water in the proximal tubule,

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- **Line 3** represents **sodium or potassium**, which is reabsorbed in concentrations approximately equal with water in the proximal tubule, resulting in no concentration change along the proximal tubule.
- **Line 4** represents **bicarbonate**, which is actively reabsorbed in the proximal tubule due to the activity of carbonic anhydrase along the brush border. This reabsorption causes the concentration of bicarbonate to decrease as fluid runs along the proximal tubule.
- **Line 5** represents **glucose or amino acids**, which are avidly reabsorbed in the proximal tubule.

In summary, the concentrations of creatinine and urea increase along the proximal tubule due to active secretion or poor reabsorption, respectively, whereas the concentrations of bicarbonate, glucose, and amino acids decrease due to active reabsorption. Sodium and potassium are reabsorbed with water in the proximal tubule, resulting in no concentration change.

Educational objective:
The concentrations of creatinine and urea increase as fluid runs along the proximal tubule, whereas the concentrations of bicarbonate, glucose, and amino acids decrease. Sodium and potassium are reabsorbed with water in the proximal tubule, resulting in no concentration change.

Physiology	Renal, Urinary Systems & Electrolytes	Nephron structure & physiology
Subject	System	Topic

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A 64-year-old man comes to the hospital due to generalized weakness and fatigue for the past several weeks. He has a history of uncontrolled hypertension and nonadherence to medical therapy. Blood pressure is 160/100 mm Hg, pulse is 90/min, and respirations are 22/min. Oxygen saturation is 95% on room air. Physical examination shows elevated jugular venous pressure, bilateral crackles, and 3+ pitting edema in both legs. Laboratory results are as follows:

Blood urea nitrogen	82 mg/dL
Creatinine	4.8 mg/dL

Which of the following additional findings are most likely present in this patient?

	pH	Bicarbonate (mEq/L)	$PaCO_2$ (mm Hg)	Anion gap (mEq/L)
A.	7.15	16	48	18
B.	7.25	12	28	20
C.	7.31	18	37	12
D.	7.32	25	50	10
E.	7.39	23	39	12

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	pH	Bicarbonate (mEq/L)	$PaCO_2$ (mm Hg)	Anion gap (mEq/L)
A. (7%)	7.15	16	48	18
✓ B. (49%)	7.25	12	28	20
C. (22%)	7.31	18	37	12
D. (11%)	7.32	25	50	10
E. (9%)	7.39	23	39	12

Omitted 49% 01 sec 05/28/2020

Explanation

Metabolic acidosis		
Type	**Normal anion gap**	**Elevated anion gap**
Mechanism	• Loss of bicarbonate	• Accumulation of unmeasured acidic compounds
Common causes	• Severe diarrhea • Renal tubular acidosis • Excessive saline infusion	• Lactic acidosis • Diabetic ketoacidosis • Renal failure (uremia) • Methanol, ethylene glycol • Salicylate toxicity

This patient's markedly elevated blood urea nitrogen (BUN) and serum creatinine in the setting of uncontrolled hypertension suggest advanced **chronic kidney disease** (CKD), a condition commonly presenting with fatigue, generalized weakness, and evidence of volume overload (eg, jugular venous distension, peripheral edema). Once CKD becomes advanced (eg, serum creatinine >3 mg/dL), **anion gap metabolic acidosis** with **respiratory compensation** is expected.

CKD involves a gradual decline in glomerular filtration rate (GFR), as evidenced by a slow increase in serum creatinine. Urea, which is formed in the liver from ammonia and other nitrogenous wastes derived from protein breakdown, is normally cleared by the kidneys and also accumulates as GFR declines. With advanced CKD, BUN levels become markedly elevated (eg, >60 mg/dL). Although urea is uncharged and does not contribute to acidemia or an elevation in the anion gap, elevated BUN (ie, **uremia**) is a marker for the reduced renal clearance and consequent **accumulation of unmeasured acidic compounds** (eg, hydrogen phosphate, hydrogen sulfate, uric acid). These compounds donate hydrogen ions (H^+) to bind up bicarbonate (HCO_3^-) and acidify the blood, and the remaining anionic component **increases the anion gap** (normal: 10-14 mEq/L).

In response to the metabolic acidosis, the lungs compensate with hyperventilation to **decrease $PaCO_2$** and help normalize pH.

(Choice A) Low pH with low HCO_3^- and elevated $PaCO_2$ represents mixed metabolic and respiratory acidosis. Such a scenario with an elevated

		• Salicylate toxicity

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In response to the metabolic acidosis, the lungs compensate with hyperventilation to **decrease $PaCO_2$** and help normalize pH.

(Choice A) Low pH with low HCO_3^- and elevated $PaCO_2$ represents mixed metabolic and respiratory acidosis. Such a scenario with an elevated anion gap may be seen with sepsis (ie, lactic acidosis) with acute respiratory failure.

(Choice C) Low pH with low HCO_3^- and slightly reduced $PaCO_2$ represents metabolic acidosis with respiratory compensation. A normal anion gap is expected with metabolic acidosis that results from loss of HCO_3^- (eg, severe diarrhea). However, this patient with CKD will have accumulation of unmeasured acidic compounds, resulting in an elevated anion gap.

(Choice D) Low pH with elevated $PaCO_2$ indicates respiratory acidosis. Minimal increase in HCO_3^- suggests acute respiratory acidosis (eg, acute opioid overdose) as there has not been time for metabolic compensation to occur (full metabolic compensation requires approximately 72 hours).

(Choice E) These acid-base and anion gap findings are within normal limits and indicate an absence of acid-base disturbance.

Educational objective:
Advanced chronic kidney disease typically involves the accumulation of unmeasured acidic compounds in the blood; therefore, anion gap metabolic acidosis with respiratory compensation is expected.

- Salicylate toxicity

Exhibit Display

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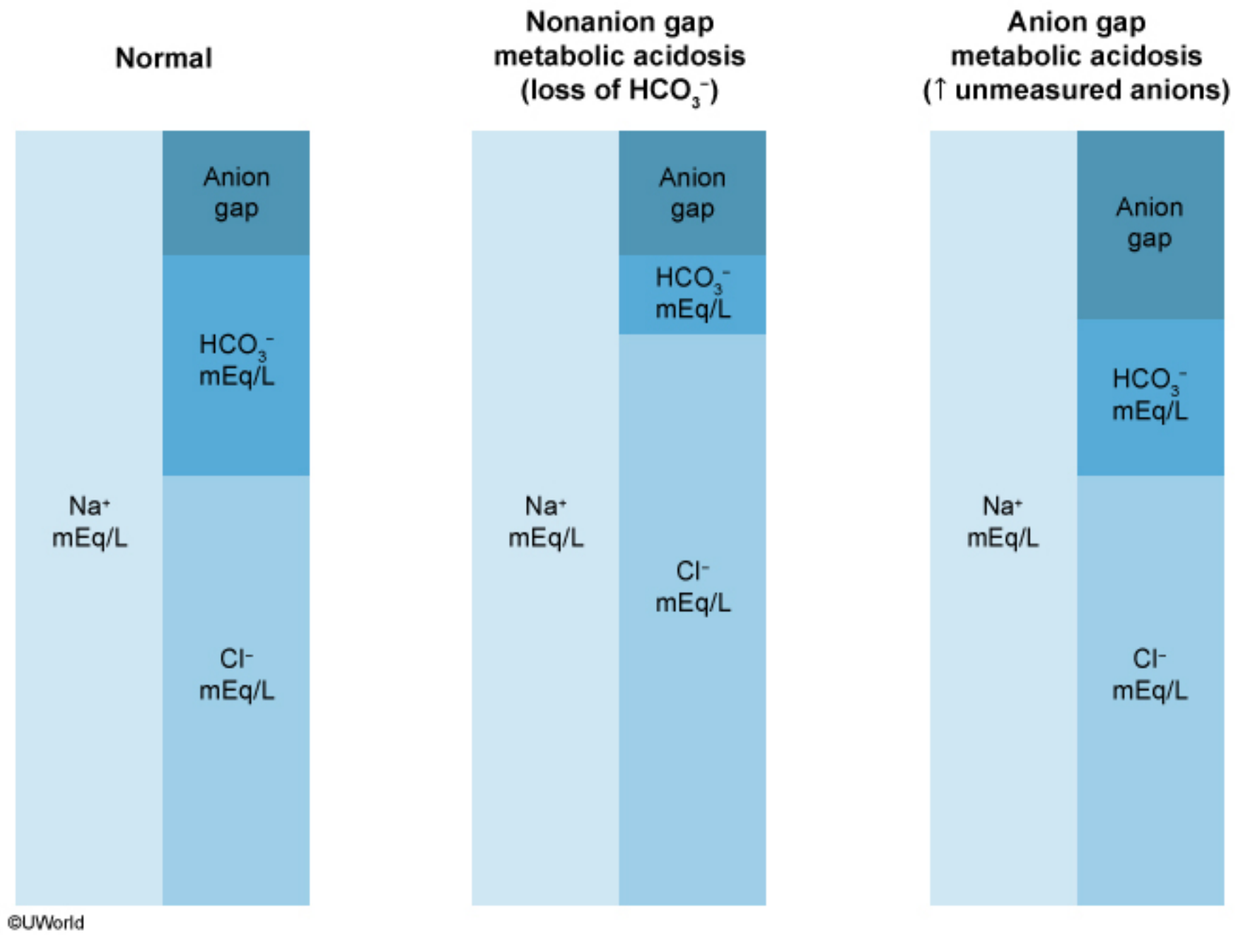
- Salicylate toxicity

Exhibit Display



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(Choice E) These acid-ba

Educational objective:
Advanced chronic kidney
metabolic acidosis with respiratory compensation is expected.

Exhibit Display

Appropriate compensatory $PaCO_2$ or bicarbonate changes in acid-base disorders

Metabolic acidosis (acute or chronic)	Expected $PaCO_2$ = (1.5 × bicarbonate) + 8 ± 2 (Winters formula)
Metabolic alkalosis (acute or chronic)	~7 mm Hg ↑ in $PaCO_2$ per 10 mEq/L ↑ in bicarbonate
Respiratory acidosis (chronic only*)	~4 mEq/L ↑ in bicarbonate per 10 mm Hg ↑ in $PaCO_2$
Respiratory alkalosis (chronic only*)	~4 mEq/L ↓ in bicarbonate per 10 mm Hg ↓ in $PaCO_2$

*Compensation for respiratory disturbances is minimal in the acute setting. The full level of chronic compensation is achieved after ~72 hr. For simplicity, normal baseline $PaCO_2$ and bicarbonate should be considered 40 mm Hg and 24 mEq/L, respectively.

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An experimental substance is infused intravenously at a constant rate into a healthy volunteer. The substance is known to selectively constrict the efferent arteriole in renal glomeruli. The rate of infusion is closely controlled during the experiment to allow for only mild constriction of the efferent arteriole. Which of the following changes in glomerular filtration rate (GFR) and filtration fraction (FF) is most likely to occur during the infusion of this substance?

A. GFR↓, FF↑

B. GFR↓, FF unchanged

C. GFR↑, FF↓

D. GFR↑, FF↑

E. GFR unchanged, FF↑

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- A. GFR↓, FF↑ (7%)
- B. GFR↓, FF unchanged (4%)
- C. GFR↑, FF↓ (6%)
- ✓ D. GFR↑, FF↑ (77%)
- E. GFR unchanged, FF↑ (3%)

Omitted
Correct answer
D

77%
Answered correctly

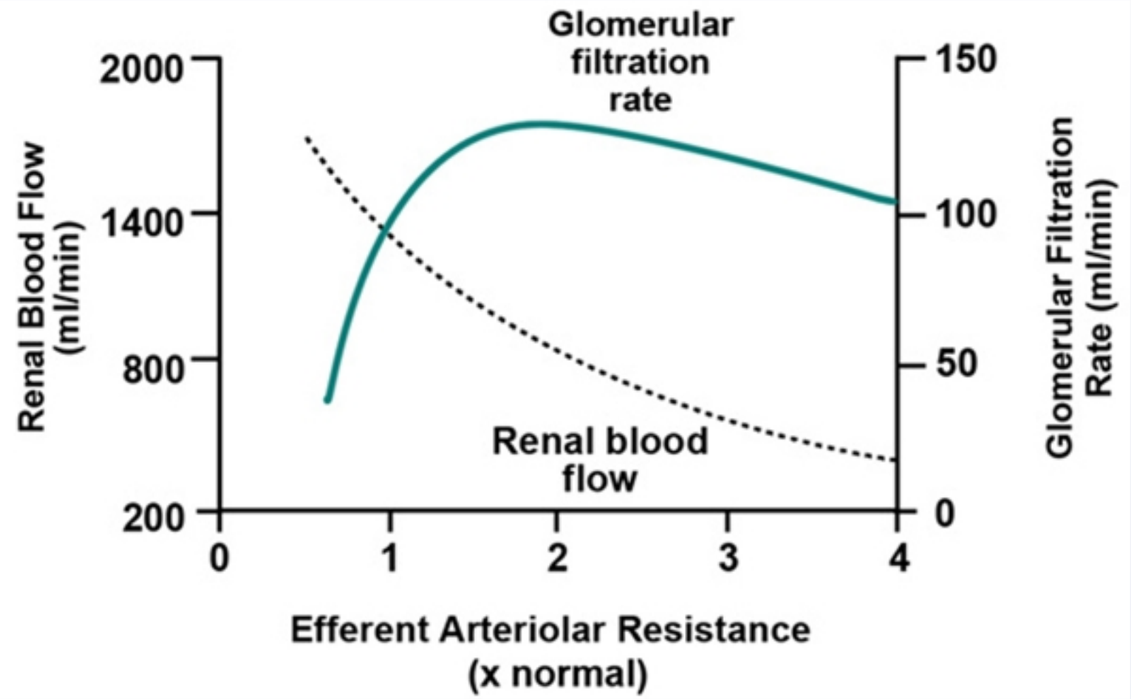
02 secs
Time Spent

06/21/2020
Last Updated

Explanation

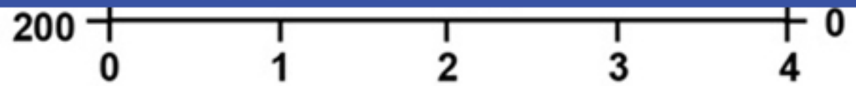
Blood circulates in the kidney along the following path: interlobar arteries→arcuate arteries→radial arteries→afferent arterioles→glomerular capillaries→efferent arterioles→peritubular capillaries→interlobar veins. Glomerular filtration rate (GFR) normally equals approximately 125 ml/min, although this number can vary between 90 to 130 by gender and between different subjects. The GFR depends on the difference in hydrostatic and oncotic pressures between the glomerular capillaries and Bowman's capsule.

Blood circulates in the kidney along the following path: interlobar arteries→arcuate arteries→radial arteries→afferent arterioles→glomerular capillaries→efferent arterioles→peritubular capillaries→interlobar veins. Glomerular filtration rate (GFR) normally equals approximately 125 ml/min, although this number can vary between 90 to 130 by gender and between different subjects. The GFR depends on the difference in hydrostatic and oncotic pressures between the glomerular capillaries and Bowman's capsule.



Constriction of the efferent arteriole produces a significant increase in glomerular capillary hydrostatic pressure because of the reduction in glomerular blood outflow. This produces a corresponding increase in GFR. Efferent arteriolar constriction also reduces renal plasma flow (RPF). The increase in GFR along with the decrease in RPF leads to an increased filtration fraction (FF) because FF=GFR/RPF (**Choice D**).

As RPF decreases, the slower capillary flow allows more time for the filtration of plasma across the glomerular membrane. This leads to an increased concentration of non-filterable plasma proteins within the glomerular capillaries, thus elevating capillary oncotic pressure. As efferent arteriolar constriction increases past a certain point, this increase in capillary oncotic pressure begins to oppose, and eventually overwhelm, the



Efferent Arteriolar Resistance (x normal)

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(Choice B) Selective constriction of the afferent arteriole decreases plasma flow into the glomerular capillaries, reducing capillary hydrostatic pressure and thus decreasing the GFR. Constriction of the afferent arteriole results in relatively equal decreases in RPF and GFR (FF=GFR/RPF), so the filtration fraction remains unchanged.

Educational objective:
Selective vasoconstriction of the efferent arteriole (up to certain extent) increases hydrostatic pressure in the glomerular capillaries, and therefore increases the glomerular filtration rate. As efferent arteriolar constriction continues to increase, the glomerular filtration rate begins to decrease due to a flow-mediated rise in oncotic pressure in the glomerular capillaries. The filtration fraction always increases with increasing efferent arteriole constriction.

Physiology	Renal, Urinary Systems & Electrolytes	GFR
Subject	System	Topic

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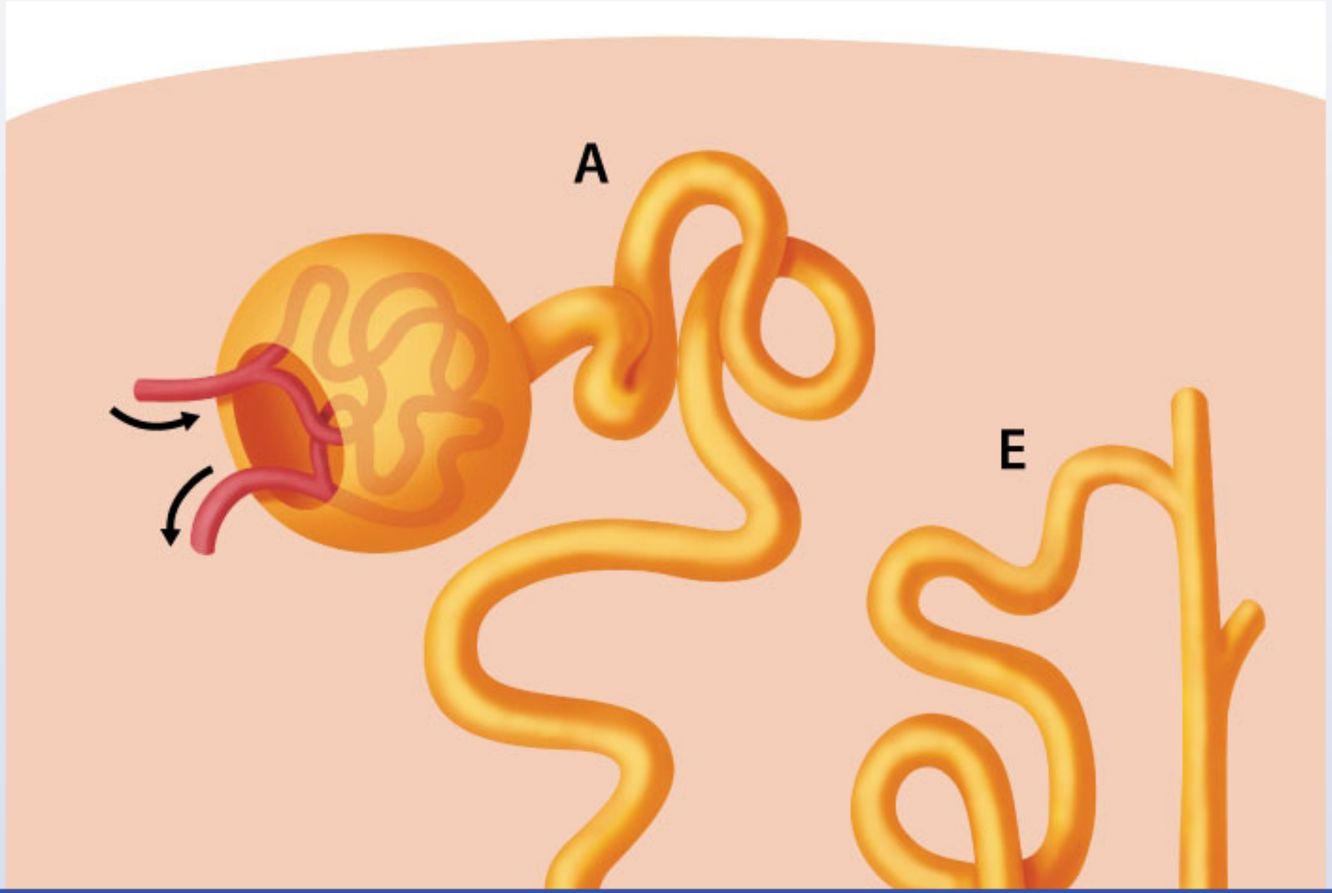
A 34-year-old woman comes to the physician complaining of frequent urination. She has tried limiting her fluid intake but found it difficult because she got very thirsty. The physician assesses the water-conserving function of her kidneys by performing a water restriction test, which shows inappropriately dilute urine. Laboratory studies drawn during the period of water deprivation show low vasopressin levels. The physician diagnoses the patient with central diabetes insipidus and explains that her kidneys are unable to absorb the proper amount of water due to defective hormone production. Which of the following areas of the nephron is normally impermeable to water regardless of serum vasopressin levels?



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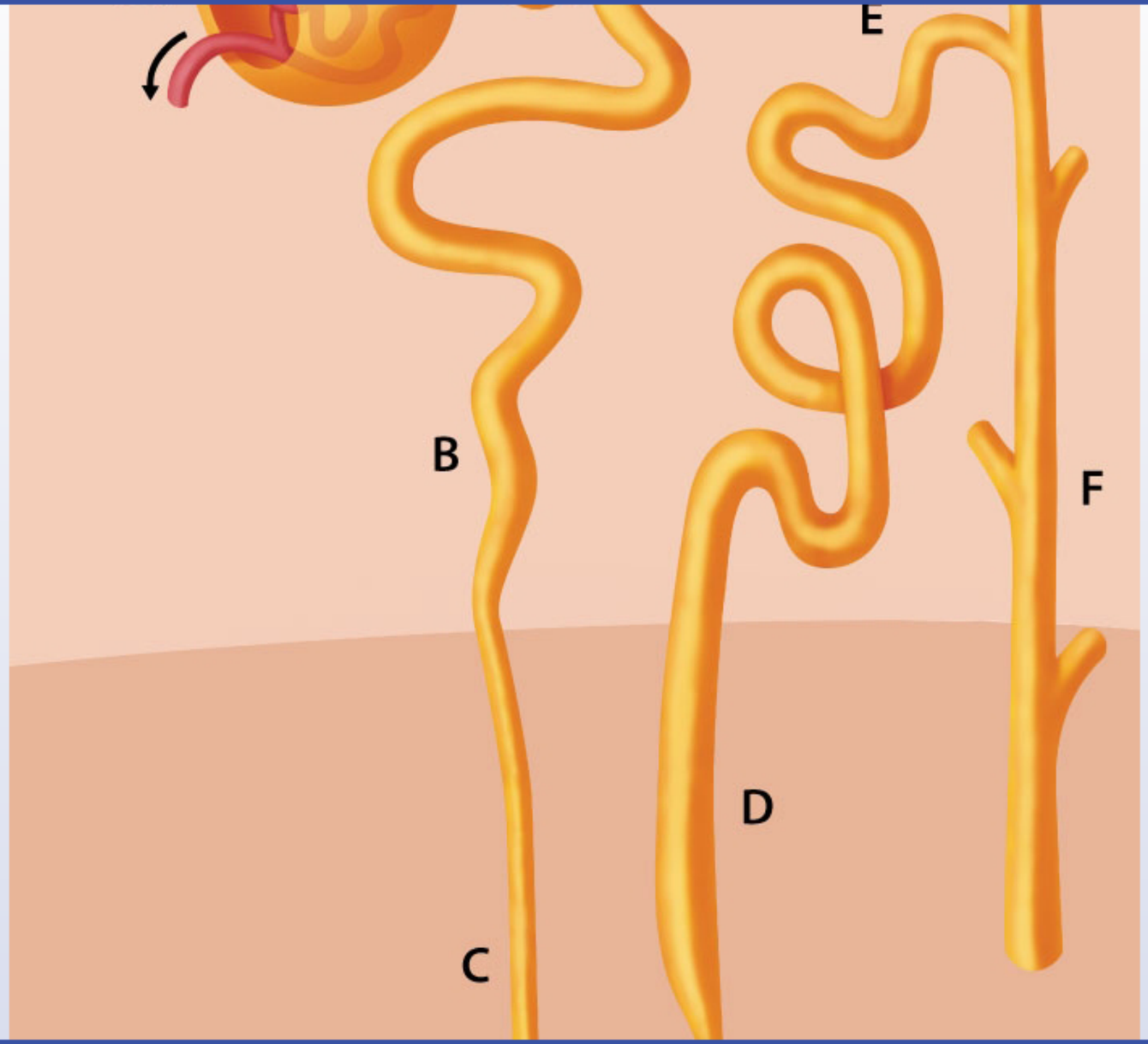

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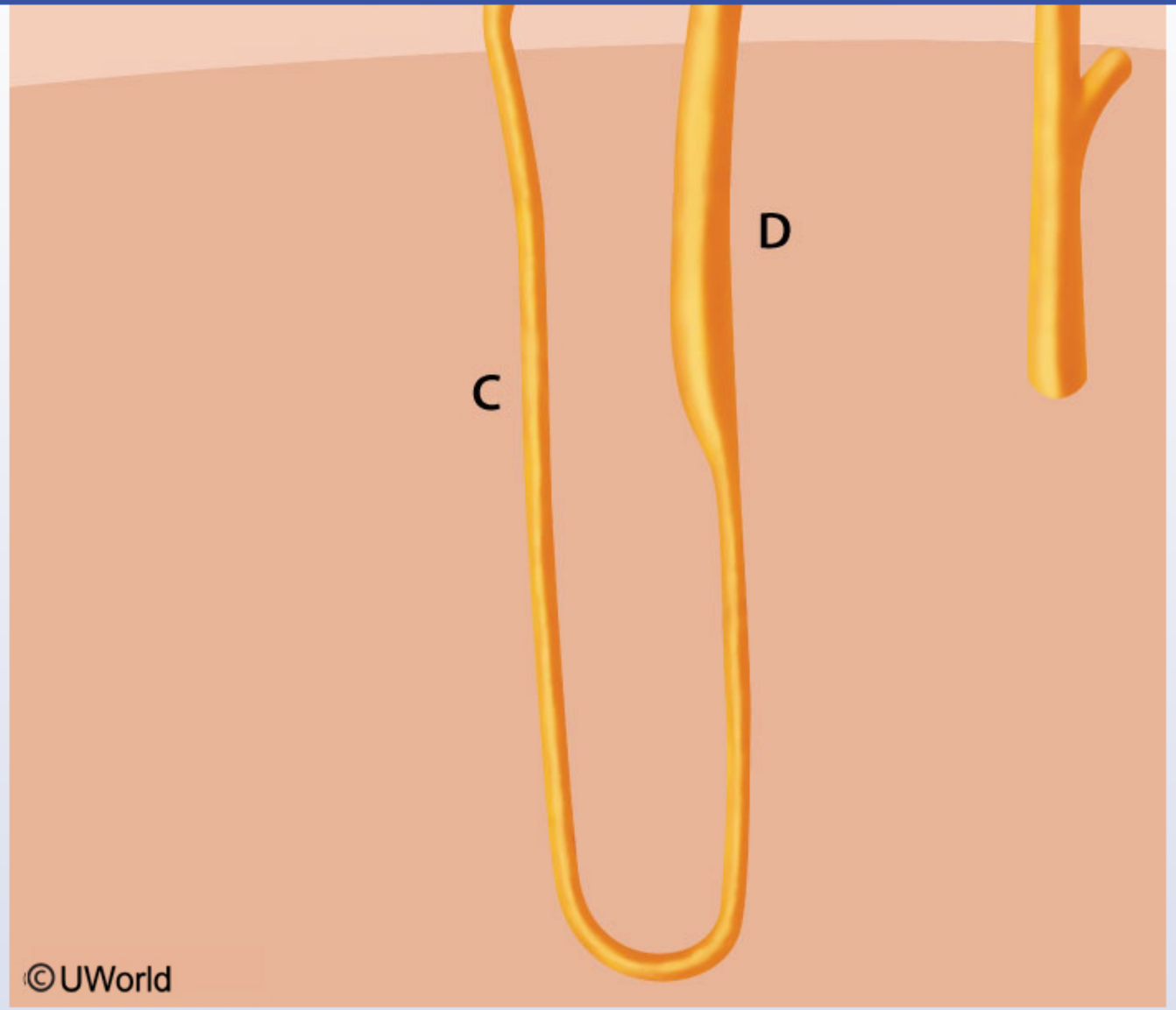

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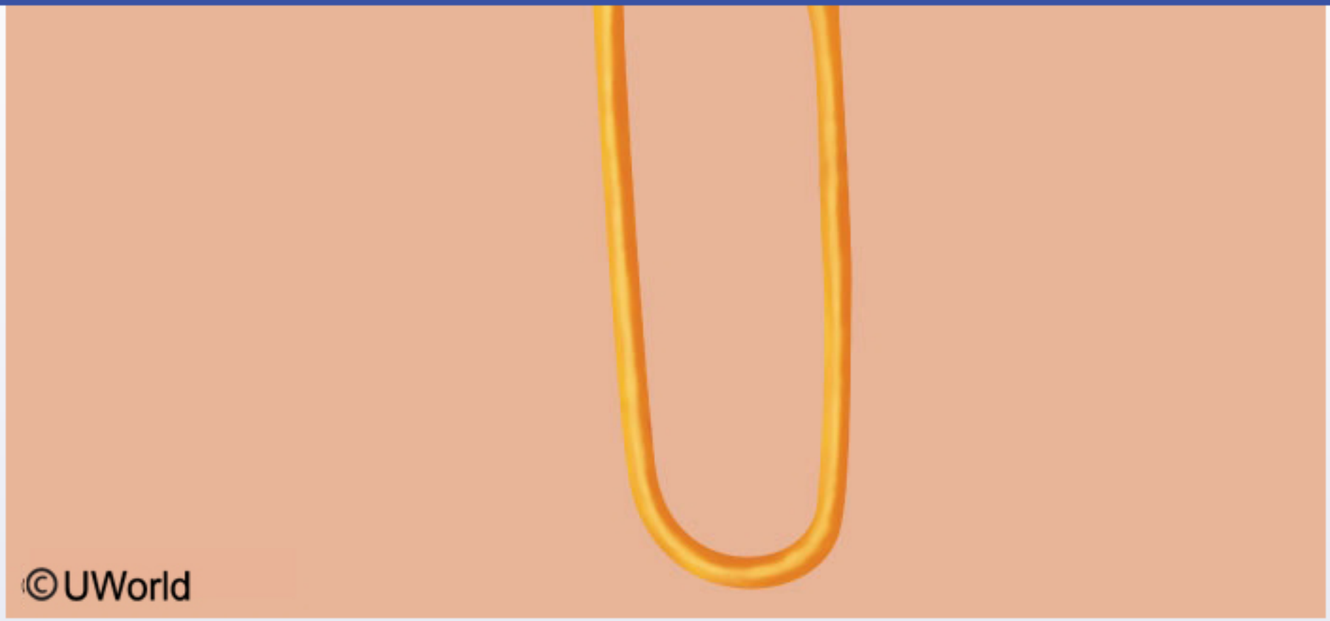

A. A

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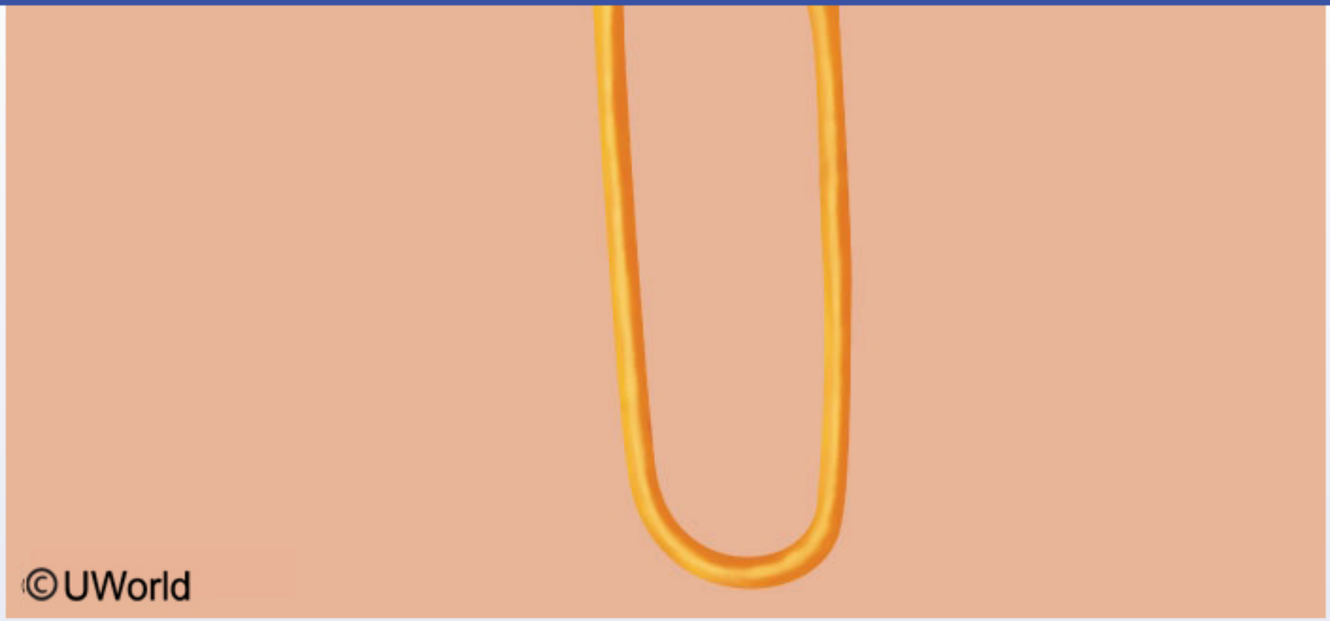

A. A (1%)
B. B (1%)
C. C (15%)
D. D (73%)
E. E (4%)
F. F (3%)

Omitted
Correct answer

73%
Answered correctly

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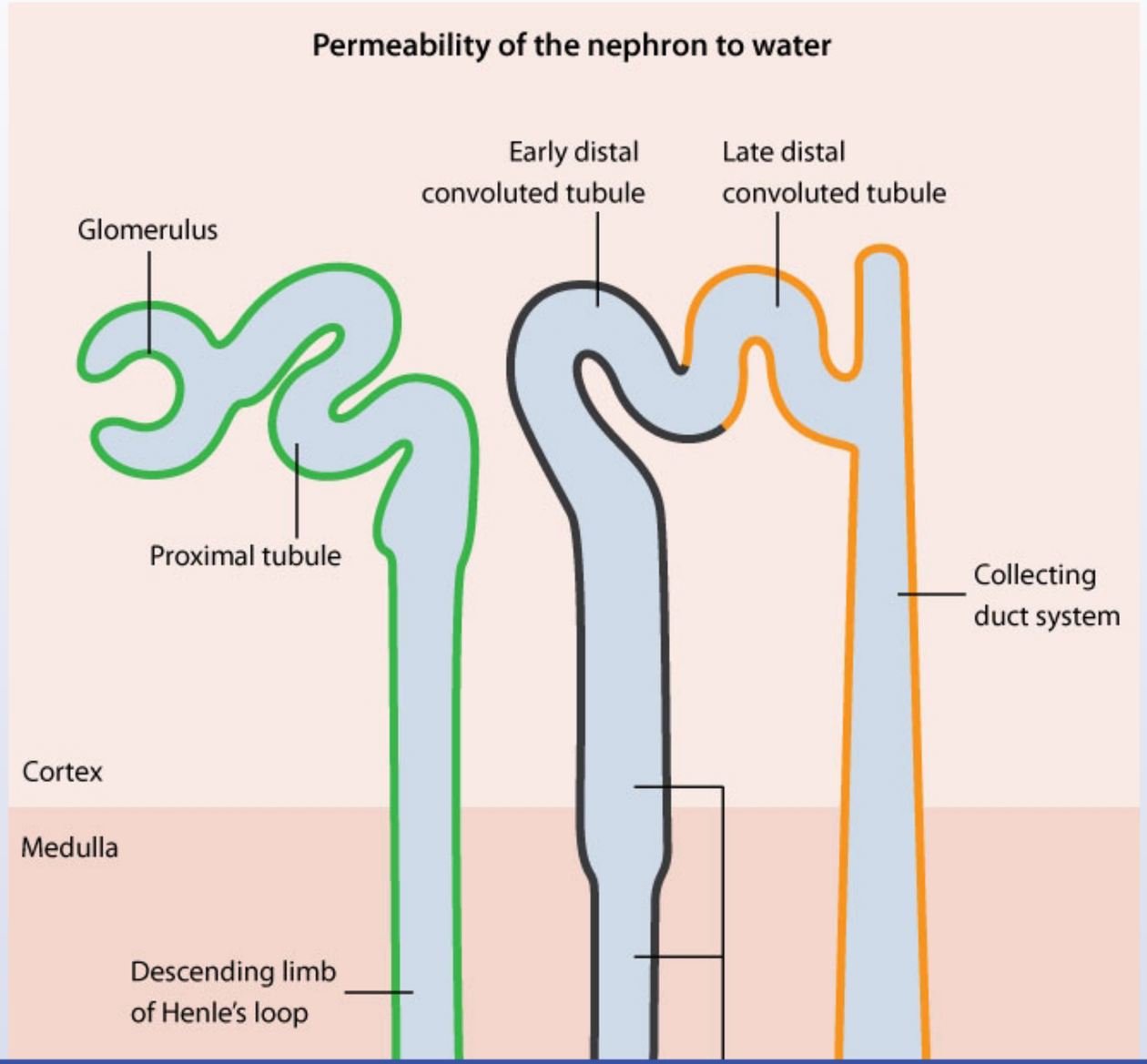

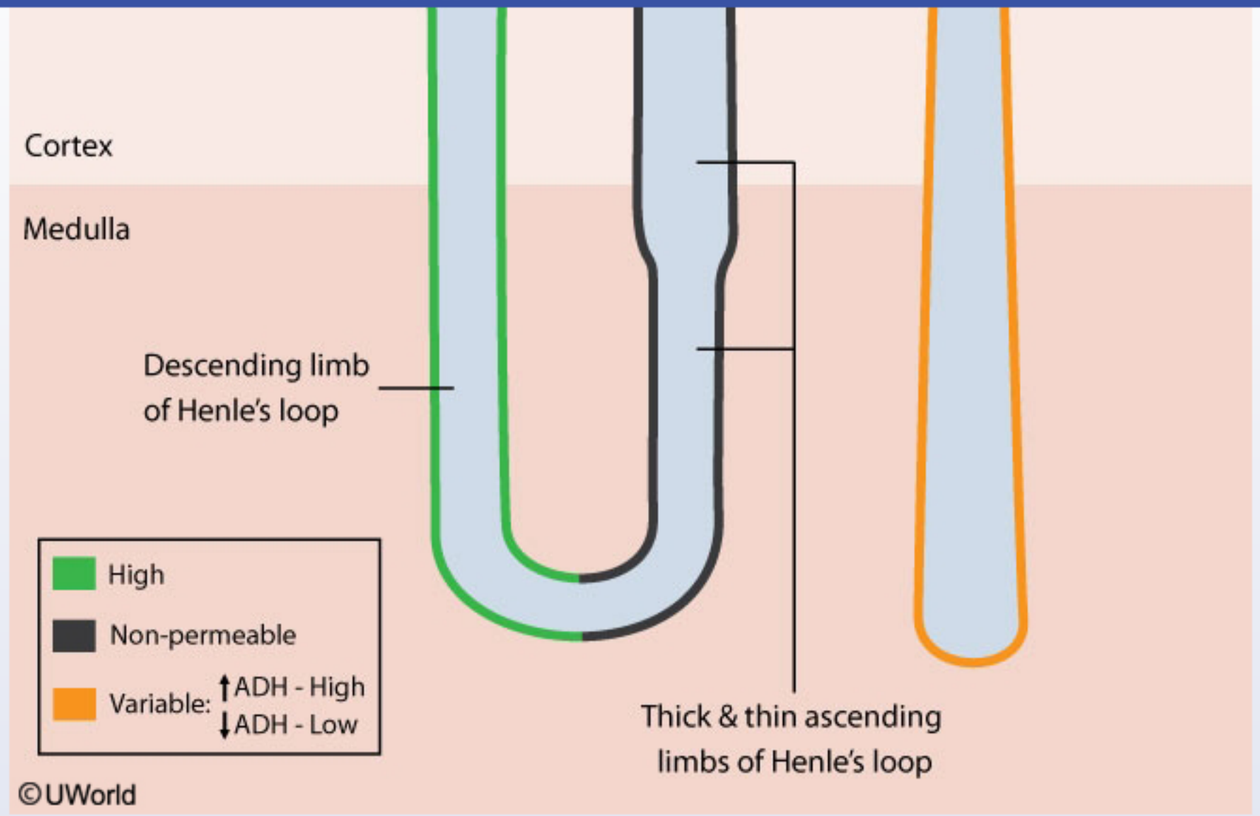

Free water excretion by the kidney depends primarily on serum vasopressin (antidiuretic hormone) levels. This hormone acts on the nephron to regulate the osmotic pressure of body fluids by varying the water permeability of the distal portion of the nephron. Water and electrolyte permeability varies in different regions of the nephron as follows:

1. Glomerular capillaries are fenestrated and therefore highly permeable to water and other solutes. The glomeruli collectively filter about 180 L of isotonic fluid (equal to plasma osmolarity) into Bowman's space daily.
2. The proximal convoluted tubule actively reabsorbs electrolytes, glucose, and amino acids. Water reabsorption in the proximal tubule occurs passively along with transport of solutes into the epithelial cells; thus, tubular fluid remains isotonic.
3. The loop of Henle is located in the renal medulla, where the interstitium is hypertonic (higher osmolarity than that of plasma). The

regulate the osmotic pressure of body fluids by varying the water permeability of the distal portion of the nephron. Water and electrolyte permeability varies in different regions of the nephron as follows:

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2. The proximal convoluted tubule actively reabsorbs electrolytes, glucose, and amino acids. Water reabsorption in the proximal tubule occurs passively along with transport of solutes into the epithelial cells; thus, tubular fluid remains isotonic.
3. The loop of Henle is located in the renal medulla, where the interstitium is hypertonic (higher osmolarity than that of plasma). The descending limb of the loop of Henle is permeable to water, but most of the ions are retained in the lumen **(Choice C)**. As water moves into the interstitium, the fluid left in the lumen becomes hypertonic.
4. The thick and thin ascending limbs of the loop of Henle are impermeable to water. In the ascending limb, the osmolarity of the tubular fluid decreases due to passive adsorption of NaCl in the thin region as well as active transport of electrolytes out of the lumen by the $Na^+/K^+/2Cl^-$ cotransporter in the thick portion.
5. Water permeability of the early distal convoluted tubule is also very low, and more electrolytes than water are reabsorbed. However, water permeability in the late distal tubule can vary based on vasopressin levels **(Choice E)**. Urinary pH is regulated chiefly through H^+ secretion by intercalated cells in the late distal and collecting tubules.
6. The water permeability of the cortical and medullary collecting ducts is also regulated by vasopressin **(Choice F)**. If the water intake of the individual is high, vasopressin is not released and water permeability of the collecting duct system is low, producing dilute urine. In contrast, water deprivation stimulates vasopressin secretion, leading to marked reabsorption of water in the collecting ducts and the production of low-volume, high-osmolar urine.

Educational objective:
The ascending limb of the loop of Henle is impermeable to water regardless of serum vasopressin levels. Reabsorption of electrolytes by the $Na^+/K^+/2Cl^-$ cotransporter occurs in the thick ascending limb and contributes to formation of the corticomedullary concentration gradient.

Physiology	Renal, Urinary Systems & Electrolytes	Diabetes insipidus
Subject	System	Topic

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A 34-year-old missionary in southern Asia is traveling to a remote village and becomes stranded when his bus breaks down. He has no access to water for 36 hours, during which his urine osmolality reaches 1100 mOsm/L. Urine concentration depends primarily on the serum level of vasopressin, which is regulated by the neurohypophysis in response to plasma osmolality and blood volume. Which of the following nephron segments responds to vasopressin by increasing absorption of a specific solute that is important for generating a high medullary concentration gradient?

A. Cortical segment of the collecting duct

B. Early distal tubule

C. Medullary segment of the collecting duct

D. Proximal tubule

E. Thin ascending limb of the loop of Henle

Submit

A 34-year-old missionary in southern Asia is traveling to a remote village and becomes stranded when his bus breaks down. He has no access to water for 36 hours, during which his urine osmolality reaches 1100 mOsm/L. Urine concentration depends primarily on the serum level of vasopressin, which is regulated by the neurohypophysis in response to plasma osmolality and blood volume. Which of the following nephron segments responds to vasopressin by increasing absorption of a specific solute that is important for generating a high medullary concentration gradient?

A. Cortical segment of the collecting duct (22%)

B. Early distal tubule (3%)

✓ C. Medullary segment of the collecting duct (60%)

D. Proximal tubule (4%)

E. Thin ascending limb of the loop of Henle (8%)

Omitted
Correct answer
C

60%
Answered correctly

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Explanation

Renal handling of urea in the setting of high ADH

Portion of the nephron
impermeable to urea

Urea

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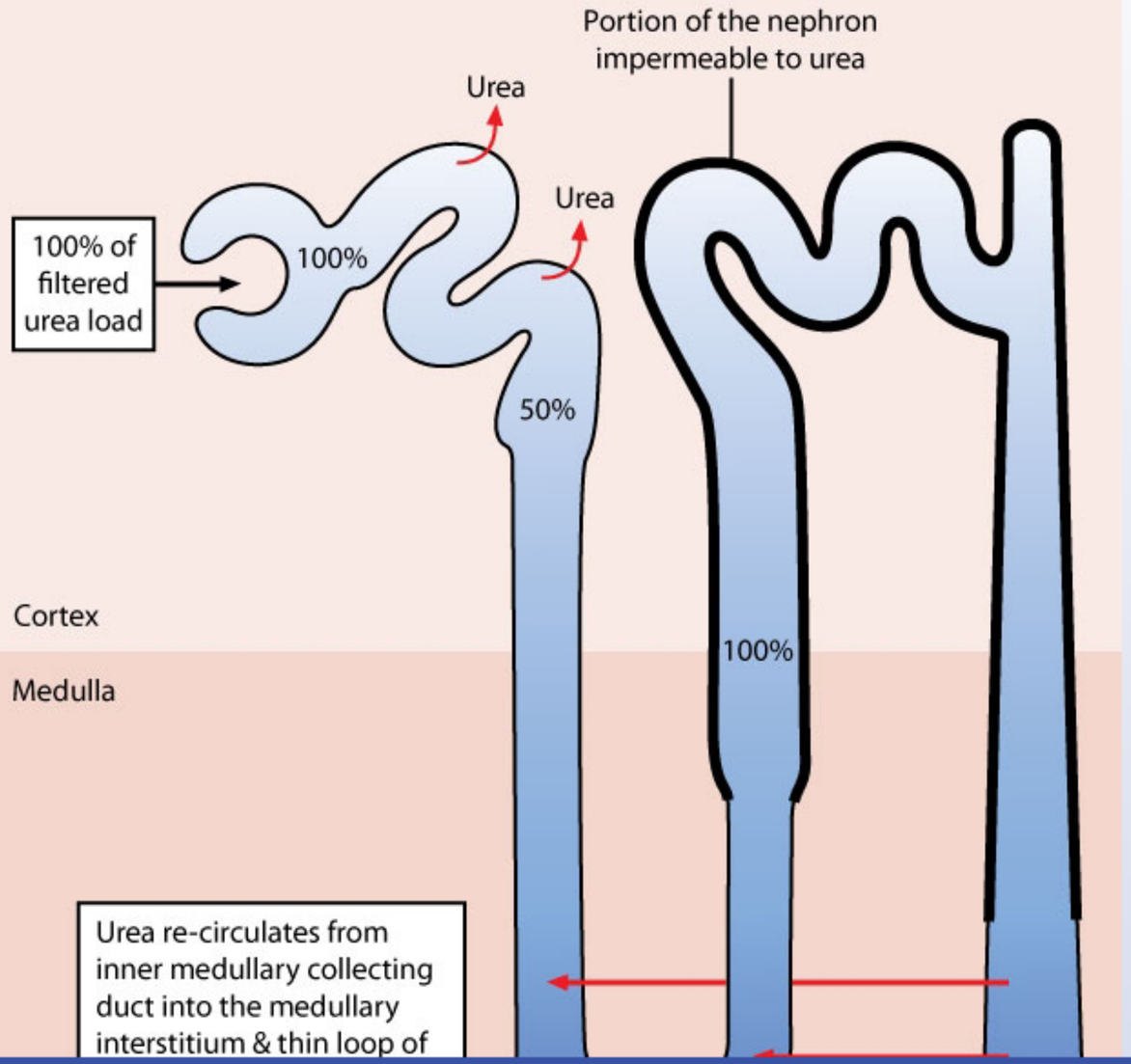
Renal handling of urea in the setting of high ADH



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Vasopressin, or antidiuretic hormone (ADH), is the primary physiologic inhibitor of free water excretion. This hormone acts on 2 major receptors, V1 and V2. Stimulation of the V1 receptor causes vasoconstriction and increased prostaglandin release; stimulation of the V2 receptor results in an antidiuretic response. ADH is secreted in response to plasma hyperosmolality and, to a lesser extent, depletion of the effective circulating volume. Water deprivation initially increases plasma osmolality, resulting in increased ADH secretion. This causes the kidney to produce concentrated urine, which helps to counteract the rise in plasma osmolality by reducing urinary free water excretion.

The medullary portion of the collecting duct is of particular importance in the production of maximally concentrated urine as the medullary interstitium is the region of highest osmolarity in the kidney. In the setting of high serum ADH levels, a large osmotic gradient drives the absorption of free water into the hypertonic medullary interstitium. As water leaves the tubular fluid, urea concentration greatly increases. ADH also increases the number of passive urea transporters in the inner medullary collecting duct, allowing a substantial fraction of the highly concentrated urea to diffuse down its concentration gradient into the medullary interstitium. When ADH levels are high, this urea resorption contributes up to 50% of total osmolarity of the medulla, further increasing the water-absorbing capacity of the nephron.

(Choice A) ADH also increases water absorption in the cortical segment of the collecting duct, reducing the amount of free water delivered to the medullary collecting duct. This prevents excess water from being absorbed into the medullary interstitium, which would otherwise dilute the osmotic gradient and reduce the maximum achievable urine concentration.

(Choice B) The early distal tubule is impermeable to both water and urea.

(Choice D) The proximal tubule is permeable to urea and resorbs about half of the filtered load. However, it does not respond to ADH.

(Choice E) The thin ascending limb of the loop of Henle is permeable to urea, which passively diffuses down its concentration gradient into the tubular lumen. Secretion of urea into the thin part of the loop of Henle allows urea to recirculate and concentrate in the tubular system, further increasing its contribution to the medullary osmotic gradient.

Educational objective:
Antidiuretic hormone acts on the medullary segment of the collecting duct to increase urea and water reabsorption, allowing for the production of maximally concentrated urine.

Physiology	Renal, Urinary Systems & Electrolytes	Urinalysis

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A 48-year-old woman is evaluated for postcoital bleeding and vaginal discharge. Pelvic examination shows a friable mass at the cervix that bleeds easily on touch. Cervical biopsy confirms invasive squamous cell cancer confined to the cervix and uterus. Lymph node metastases are not seen. A radical hysterectomy is performed during which the right ureter is accidentally injured but then repaired. Imaging studies performed after the surgery show a partial obstruction of the right ureter with mild dilation of the proximal collecting system. Which of the following changes are most likely to be seen in the right kidney?

	Glomerular Filtration Rate	Filtration Fraction
A.	No change	↑
B.	↑	↓
C.	↓	↑
D.	↓	No change
E.	↓	↓

Submit

A 48-year-old woman is evaluated for postcoital bleeding and vaginal discharge. Pelvic examination shows a friable mass at the cervix that bleeds easily on touch. Cervical biopsy confirms invasive squamous cell cancer confined to the cervix and uterus. Lymph node metastases are not seen. A radical hysterectomy is performed during which the right ureter is accidentally injured but then repaired. Imaging studies performed after the surgery show a partial obstruction of the right ureter with mild dilation of the proximal collecting system. Which of the following changes are most likely to be seen in the right kidney?

	Glomerular Filtration Rate	Filtration Fraction
A. (5%)	No change	↑
B. (5%)	↑	↓
C. (9%)	↓	↑
D. (12%)	↓	No change
✓ E. (67%)	↓	↓

Omitted
Correct answer
E

67%
Answered correctly

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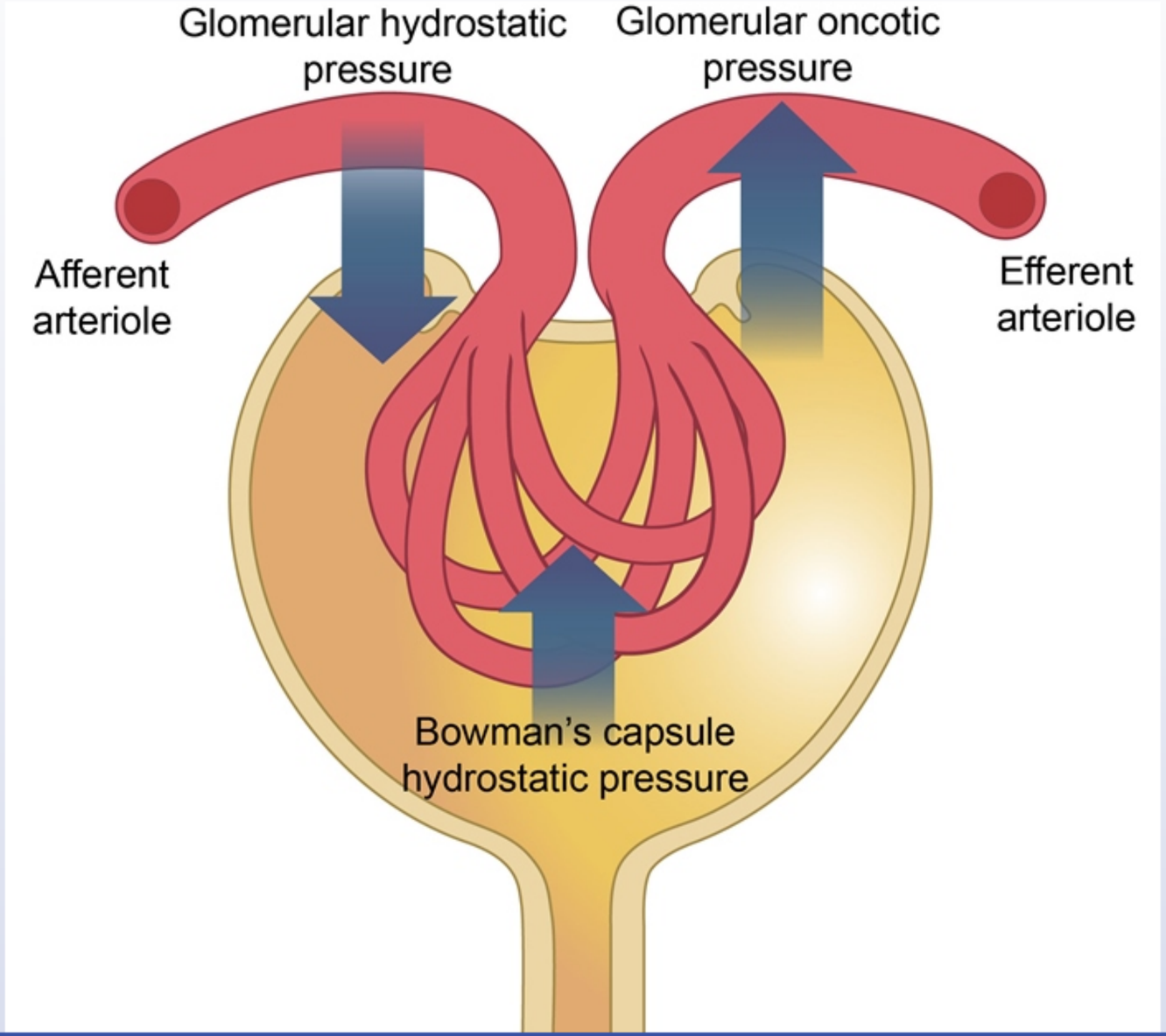
Explanation


Glomerular hydrostatic pressure
Glomerular oncotic pressure
Afferent arteriole
Efferent arteriole
Bowman's capsule hydrostatic pressure

The glomerular filtration rate (GFR) depends on the interplay of hydrostatic and oncotic pressures in the glomerular capillaries and Bowman's space. The GFR increases with higher glomerular hydrostatic pressure and decreases with increasing Bowman's capsule hydrostatic pressure or higher glomerular capillary oncotic pressure. Acute **ureteral obstruction** increases hydrostatic pressure proximal to the constriction. This pressure rise is transmitted back to the Bowman's space, resulting in **decreased GFR**.

The filtration fraction (FF) is the portion of the renal plasma flow (RPF) that is filtered from the glomerular capillaries into Bowman's space (ie, the GFR:RPF ratio). With acute ureteral obstruction (first 12 hours), the RPF may transiently increase; however, with time, efferent arteriolar constriction (in response to reduced GFR) will decrease RPF. Even at later stages, though, the GFR remains depressed to a greater extent than the RPF, resulting in **reduced FF**.

Educational objective:
Acute ureteral constriction or obstruction decreases the glomerular filtration rate and filtration fraction.

References

- Renal hemodynamics in acute unilateral ureteral obstruction: contribution of endothelium-derived relaxing factor.

Physiology	Renal, Urinary Systems & Electrolytes	GFR
Subject	System	Topic

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A 28-year-old woman, gravida 1 para 0, at 12 weeks gestation comes to the office for follow-up. During the first trimester, the patient had mild nausea, which has now resolved, and the patient feels well. She has a history of epilepsy for which she is taking lamotrigine; her only other medication is a prenatal vitamin with folic acid. Vital signs and physical examination show no abnormalities. Fetal heart tones are normal. In addition to routine prenatal care, the patient's serum lamotrigine level is being closely monitored because the drug is eliminated primarily by the kidneys. Which of the following renal changes are expected in this patient during her pregnancy?

	Renal blood flow	Glomerular filtration rate	Serum creatinine level
A.	Decreased	Decreased	Increased
B.	Decreased	Unchanged	Decreased
C.	Increased	Decreased	Unchanged
D.	Increased	Increased	Decreased
E.	Unchanged	Increased	Increased

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	Renal blood flow	Glomerular filtration rate	Serum creatinine level
A. (16%)	Decreased	Decreased	Increased
B. (1%)	Decreased	Unchanged	Decreased
C. (9%)	Increased	Decreased	Unchanged
✓ D. (61%)	Increased	Increased	Decreased
E. (10%)	Unchanged	Increased	Increased

Omitted
Correct answer
D

61%
Answered correctly

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06/04/2020
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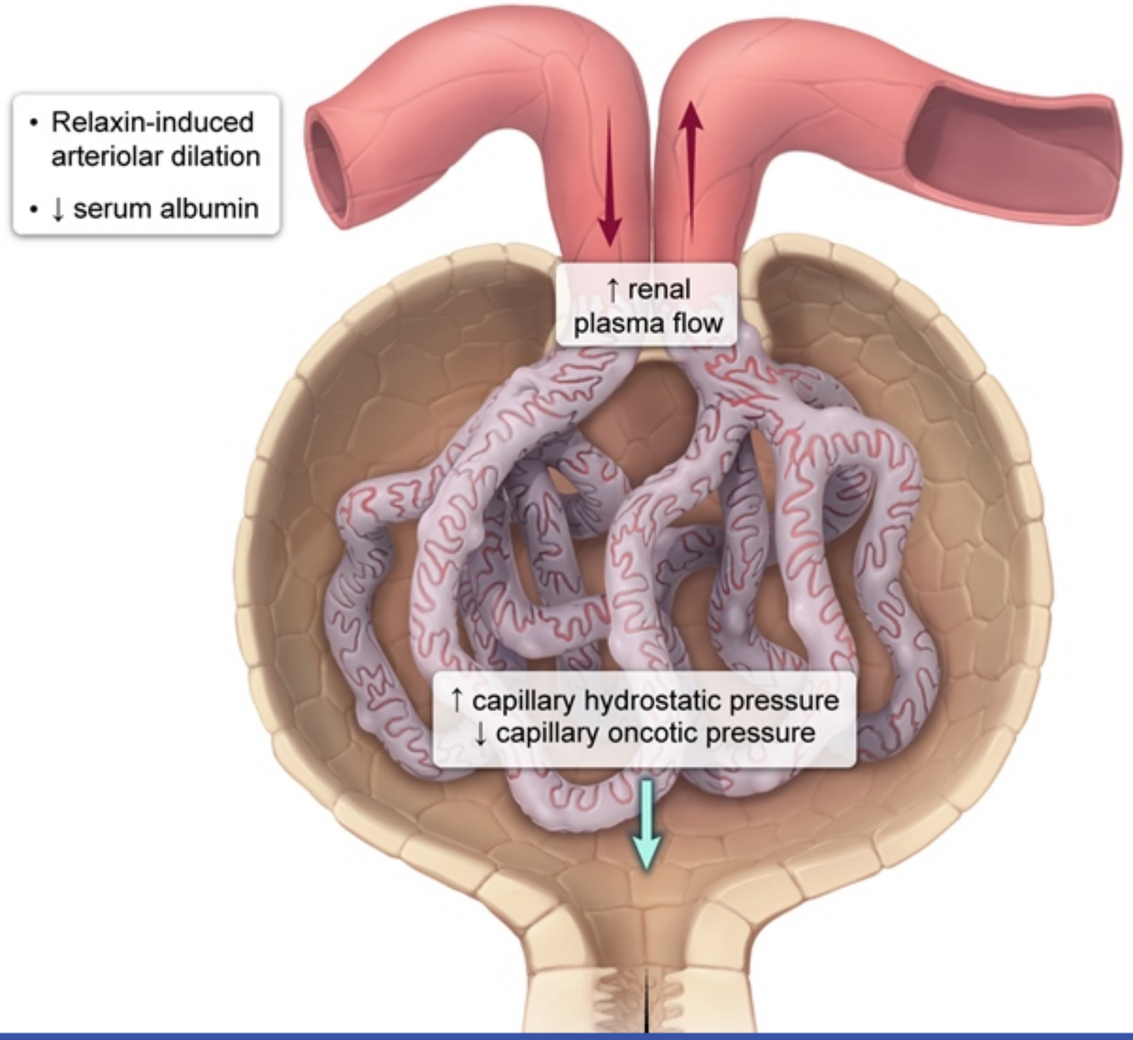
Explanation

Explanation

Renal adaptations during pregnancy



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Increased GFR
Increased creatinine clearance

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Pregnancy results in multiple maternal hemodynamic changes that affect renal physiology. Marked **volume expansion** occurs due to renin release from extrarenal sources (eg, ovaries, decidua) with upregulation of the renin-angiotensin-aldosterone system (RAAS). Despite the increased sodium and water retention and RAAS activity, pregnancy is marked by **widespread vasodilation** and increased arterial compliance, likely due to the release of relaxin and reduced sensitivity to angiotensin II and norepinephrine.

Increased blood volume and cardiac output result in the following alterations in renal hemodynamics:

- **Increased renal plasma flow (RPF)**, which peaks at 12 weeks gestation.
- **Increased glomerular filtration rate**, which is largely driven by the increased RPF. However, later in gestation, the dilutional reduction in serum albumin levels results in lower plasma oncotic pressure and further promotes filtration.

These alterations result in increased creatinine clearance, leading to **decreased serum creatinine levels**, typically by an average reduction of approximately 0.4 mg/dL. Therefore, serum creatinine levels considered normal in nonpregnant patients (eg, 1.0 mg/dL) represent significant renal dysfunction in this population. Furthermore, a small rise in creatinine in a pregnant woman reflects a marked reduction in renal function.

(Choices A, B, C, and E) These hemodynamic alterations would not occur in normal pregnancy and represent renal dysfunction in a pregnant patient.

Educational objective:
Pregnancy results in significant plasma expansion and widespread vasodilation, leading to increased renal plasma flow and glomerular filtration rates. Serum creatinine is reduced by approximately 0.4 mg/dL in this population; therefore, a rise in serum creatinine, even to levels that are normal in nonpregnant patients, represents significant renal dysfunction.

Physiology	Renal, Urinary Systems & Electrolytes	GFR
Subject	System	Topic

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A 45-year-old man with a history of chronic alcohol use disorder is brought to the emergency room due to altered mental status. The patient appears malnourished. He is given thiamine, folic acid, a multivitamin, and dextrose-containing intravenous fluids. However, the patient develops marked muscle weakness a few hours later. Laboratory studies reveal a serum phosphate concentration of 0.5 mg/dL (normal: 2.5-4.5). Which of the following is the most likely cause of this patient's low serum phosphate level?

A. Decreased renal proximal tubular reabsorption

B. Increased colonic excretion of phosphate

C. Increased extracellular binding with calcium

D. Increased uptake by bone cells

E. Redistribution of phosphate into hepatic and muscle cells

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A. Decreased renal proximal tubular reabsorption (25%)

B. Increased colonic excretion of phosphate (5%)

C. Increased extracellular binding with calcium (20%)

D. Increased uptake by bone cells (3%)

✓ E. Redistribution of phosphate into hepatic and muscle cells (45%)

Omitted
Correct answer
E

45%
Answered correctly

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Explanation

Causes of hypophosphatemia	
Internal redistribution	• Increased insulin secretion (especially refeeding malnourished patients) • Acute respiratory alkalosis (stimulates glycolysis) • Hungry bone syndrome (after parathyroidectomy)
	• Chronic poor intake

Explanation

Causes of hypophosphatemia	
Internal redistribution	• Increased insulin secretion (especially refeeding malnourished patients) • Acute respiratory alkalosis (stimulates glycolysis) • Hungry bone syndrome (after parathyroidectomy)
Decreased intestinal absorption	• Chronic poor intake • Aluminum- or magnesium-containing antacids (bind phosphate) • Steatorrhea or chronic diarrhea
Increased urinary excretion	• Primary & secondary hyperparathyroidism • Vitamin D deficiency (↓ GI absorption, ↑ urinary excretion) • Primary renal phosphate wasting syndromes • Fanconi syndrome

Phosphorus is involved in multiple biologic processes, including cellular energy metabolism, bone formation, and acid-base homeostasis. Although biologically active phosphorus is largely found intracellularly, serum phosphorus levels are often reflective of available body stores and are maintained through the action of hormones (eg, parathyroid hormone, calcitriol, FGF-23) on the small intestines, bones, and kidneys.

Malnourishment (eg, due to chronic alcohol use disorder) results in the depletion of phosphate, although serum levels may remain normal due to transcellular shifts. Reintroduction of **carbohydrates** (ie, dextrose-containing intravenous fluids) increases insulin secretion, which stimulates the **redistribution of phosphate** from the serum **into muscle and hepatic cells** for use during glycolysis (eg, **formation of ATP**, 2-3 diphosphoglycerate). This leads to profound hypophosphatemia; lack of adequate intracellular phosphate can result in failure of cellular energy metabolism, producing the clinical features of refeeding syndrome (eg, **muscular weakness**, arrhythmias, congestive heart failure).

(Choice A) Increased parathyroid hormone reduces the proximal tubular reabsorption of phosphorus. Although hyperparathyroidism results in hypophosphatemia, this occurs over a prolonged period and would not occur acutely after infusion of dextrose-containing fluids.

Although biologically active phosphorus is largely found intracellularly, serum phosphorus levels are often reflective of available body stores and are maintained through the action of hormones (eg, parathyroid hormone, calcitriol, FGF-23) on the small intestines, bones, and kidneys.

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(Choice A) Increased parathyroid hormone reduces the proximal tubular reabsorption of phosphorus. Although hyperparathyroidism results in hypophosphatemia, this occurs over a prolonged period and would not occur acutely after infusion of dextrose-containing fluids.

(Choice B) Although chronic diarrhea can cause hypophosphatemia, it predominantly occurs from reduced intestinal absorption of phosphorus, not increased excretion (only a small fraction of total body phosphorus is excreted into the intestines and lost in the feces). Furthermore, this patient is not having diarrhea.

(Choice C) Phosphorus can combine with calcium to form salts, which can be deposited in the skin or other organs (ie, dystrophic calcification). However, this typically occurs in the setting of hyperphosphatemia (not hypophosphatemia) in end-stage renal disease.

(Choice D) Hungry bone syndrome causes hypophosphatemia and hypocalcemia due to the rapid formation of bone after parathyroidectomy in a patient with chronic hyperparathyroidism. However, significant hypocalcemia typically results in tetany, not diffuse weakness, and this disorder usually occurs in the early postoperative period (2-4 days).

Educational objective:
Refeeding syndrome occurs after the reintroduction of carbohydrates in patients with chronic malnourishment, which stimulates insulin secretion and drives phosphorus intracellularly in an effort to maintain cellular energy metabolism (eg, ATP production); this redistribution of phosphorus can result in severe hypophosphatemia.

Physiology	Renal, Urinary Systems & Electrolytes	Hypophosphatemia
Subject	System	Topic

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A study is conducted to standardize laboratory equipment in a hospital network. In one hospital, 2 healthy volunteers undergo testing. Both are found to have a serum creatinine level of 1.1 mg/dL. Glomerular filtration rate is estimated using the same equation and reveals values of 118 mL/min in one volunteer and 70 mL/min in the other. A difference in which of the following parameters best explains the observed laboratory findings in these volunteers?

A. Basal metabolic rate

B. Dietary purine intake

C. Hepatic synthetic function

D. Renal tubular reabsorption capacity

E. Skeletal muscle mass

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A. Basal metabolic rate (11%)

B. Dietary purine intake (4%)

C. Hepatic synthetic function (4%)

D. Renal tubular reabsorption capacity (25%)

✓ E. Skeletal muscle mass (54%)

Omitted
Correct answer
E

54%
Answered correctly

02 secs
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04/28/2020
Last Updated

Explanation

Creatinine is a waste product generated by the breakdown of creatine in the muscles. It is released from muscle at a relatively constant rate, is neither metabolized nor reabsorbed by the kidneys, and is easily measured; therefore, it can be used to **estimate the glomerular filtration rate** (GFR).

However, creatinine has several **limitations** in the estimation of GFR. Because its formation is due largely to muscle metabolism, **differences in skeletal muscle mass** (eg, higher in body builders and lower in elderly patients, those with amputations) **affect the amount of creatinine synthesized**. Alterations in **dietary intake** can also raise (eg, creatine supplements, high-meat diet) or lower (eg, low-protein vegetarian diet)

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However, creatinine has several **limitations** in the estimation of GFR. Because its formation is due largely to muscle metabolism, **differences in skeletal muscle mass** (eg, higher in body builders and lower in elderly patients, those with amputations) **affect the amount of creatinine synthesized**. Alterations in **dietary intake** can also raise (eg, creatine supplements, high-meat diet) or lower (eg, low-protein vegetarian diet) creatinine levels. Therefore, patients with lower muscle mass or reduced dietary meat intake may have significantly lower GFRs for any given creatinine level.

Another potential source of error is the active secretion of creatinine by the proximal tubules; if uncorrected, this results in a slight overestimation of GFR (~10%-20%).

(Choice A) Alterations in basal metabolic rate can explain why individuals can have the same caloric intake but different body weight. However, they do not affect creatinine levels, which is dependent on muscle mass and dietary meat intake.

(Choice B) Increased levels of dietary purines can result in gout formation in predisposed individuals but are not associated with altered creatinine formation.

(Choice C) Creatine (creatinine precursor) is a nonessential nutrient synthesized in the liver and kidney and also obtained from meat consumption; although a disruption in hepatic synthetic function could reduce endogenous creatine production by the liver, continued production by the kidney along with creatine obtained from the diet make hepatic dysfunction alone an unlikely source of altered creatine/creatinine levels.

(Choice D) Creatinine is freely filtered and neither metabolized nor reabsorbed by the kidneys; therefore, tubular reabsorptive function would not affect the GFR.

Educational objective:
Creatinine, a waste product generated by the breakdown of creatine in the muscles, is used to estimate the glomerular filtration rate (GFR). Creatinine formation is dependent on muscle mass and meat intake; therefore, patients with low muscle mass (eg, elderly patient, those with amputations) or low intake (eg, low-protein vegetarian diet) can have significantly lower GFRs for any given creatinine level.

However, creatinine has several **limitations** in the estimation of GFR. Because its formation is due largely to muscle metabolism, **differences in skeletal muscle mass** (eg, higher in body builders and lower in elderly patients, those with amputations) **affect the amount of creatinine synthesized**. Alterations in **dietary intake** can also raise (eg, creatine supplements, high-meat diet) or lower (eg, low-protein vegetarian diet) creatinine levels. Therefore, patients with lower muscle mass or reduced dietary meat intake may have significantly lower GFRs for any given creatinine level.

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Physiology	Renal, Urinary Systems & Electrolytes	Chronic kidney disease
Subject	System	Topic

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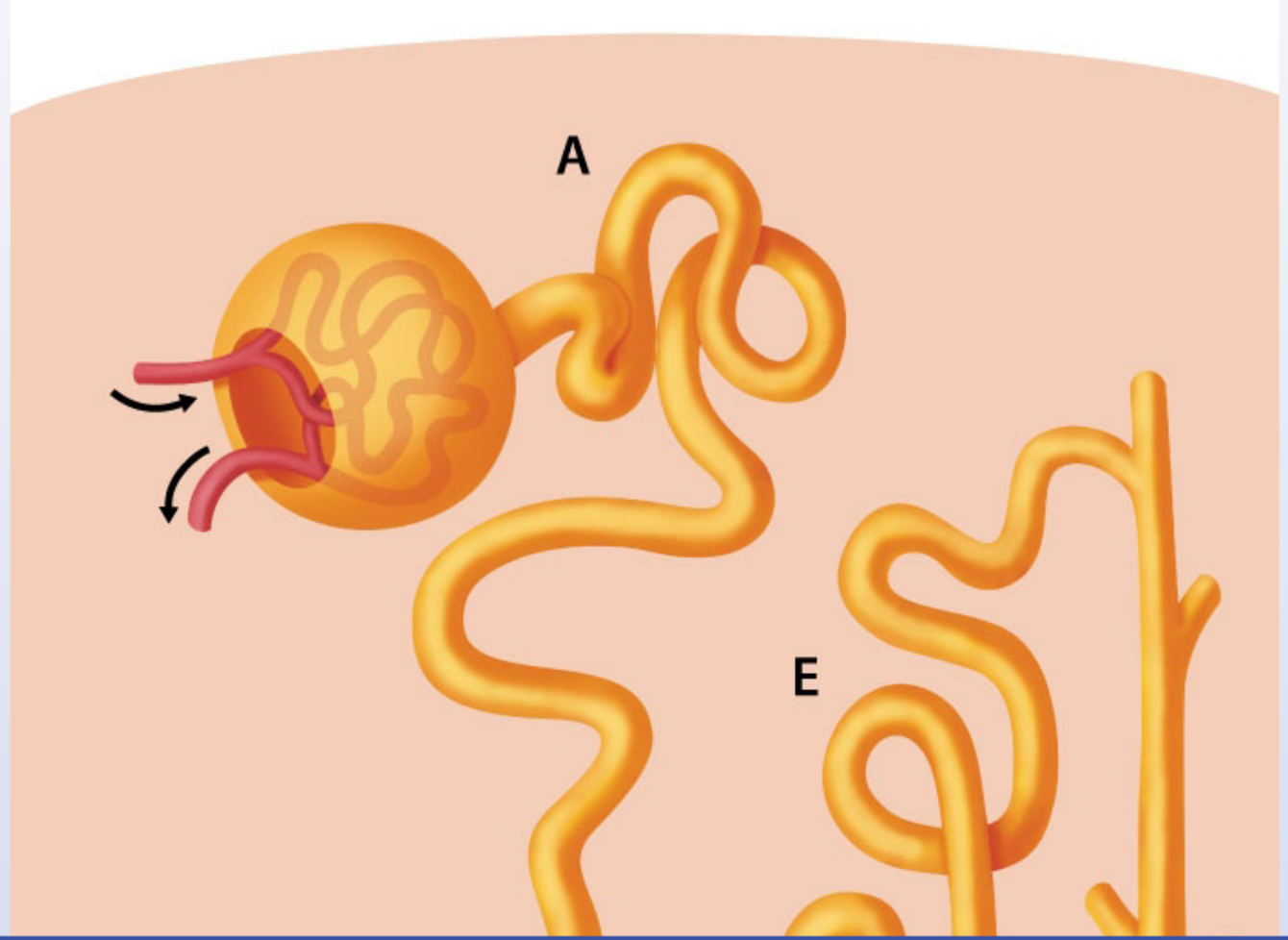
Nephrologists at a research hospital are investigating the physiologic changes that occur in diabetes insipidus. The group develops a technique that permits sampling of tubular urine in experimental animals with physiology similar to that of humans. The animals then undergo hypophysectomy, after which tubular fluid samples are obtained from multiple sites throughout the nephron. In the absence of antidiuretic hormone, fluid from which of the following sampling sites is most likely to have the highest osmolarity?



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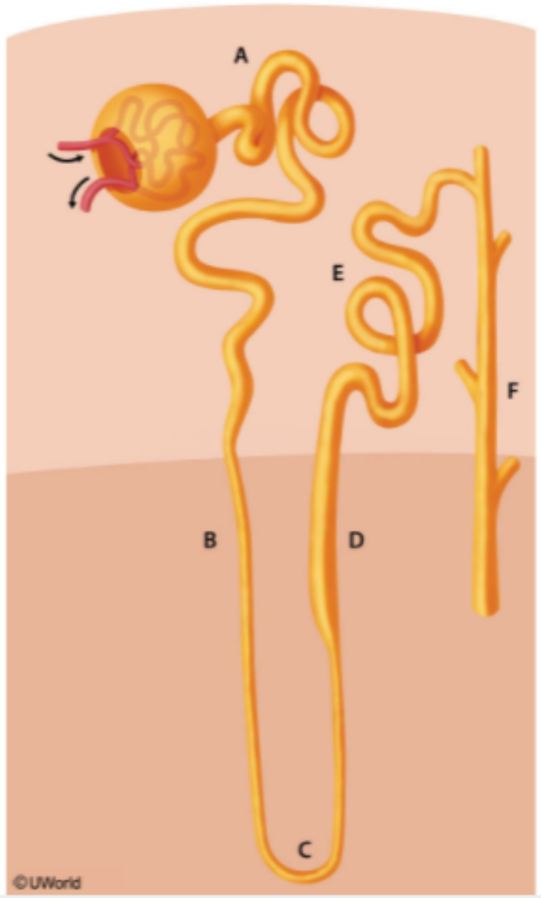

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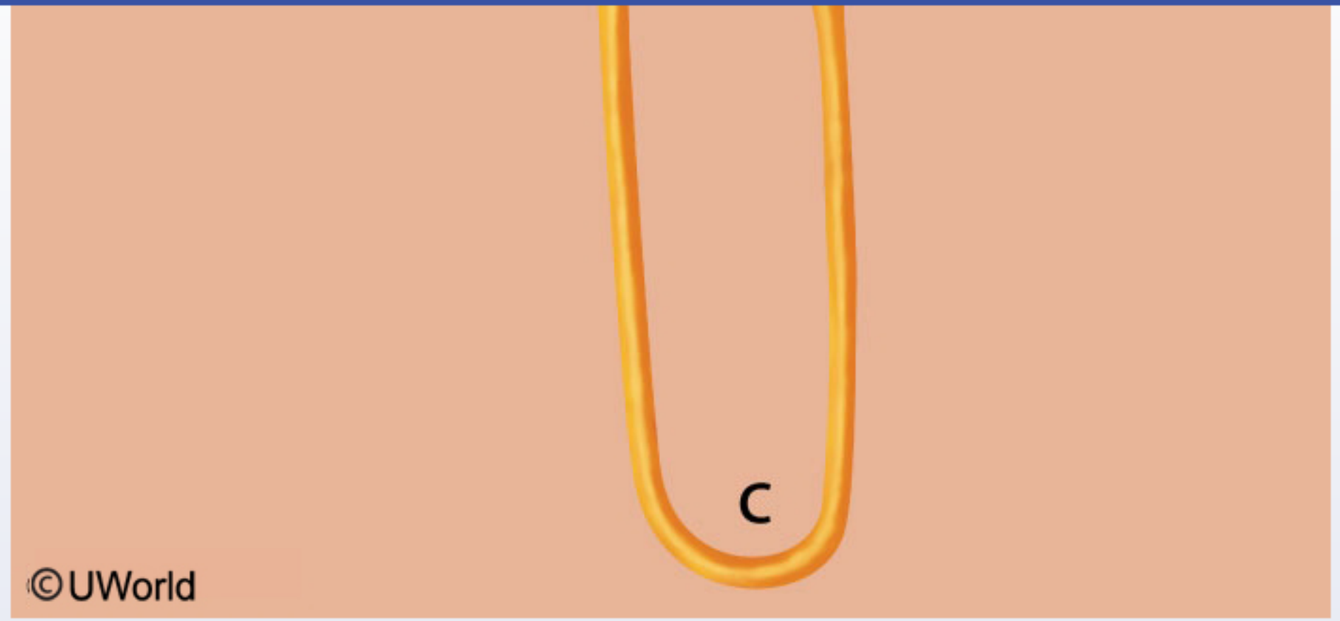

A. A
B. B
C. C
D. D
E. E
F. F

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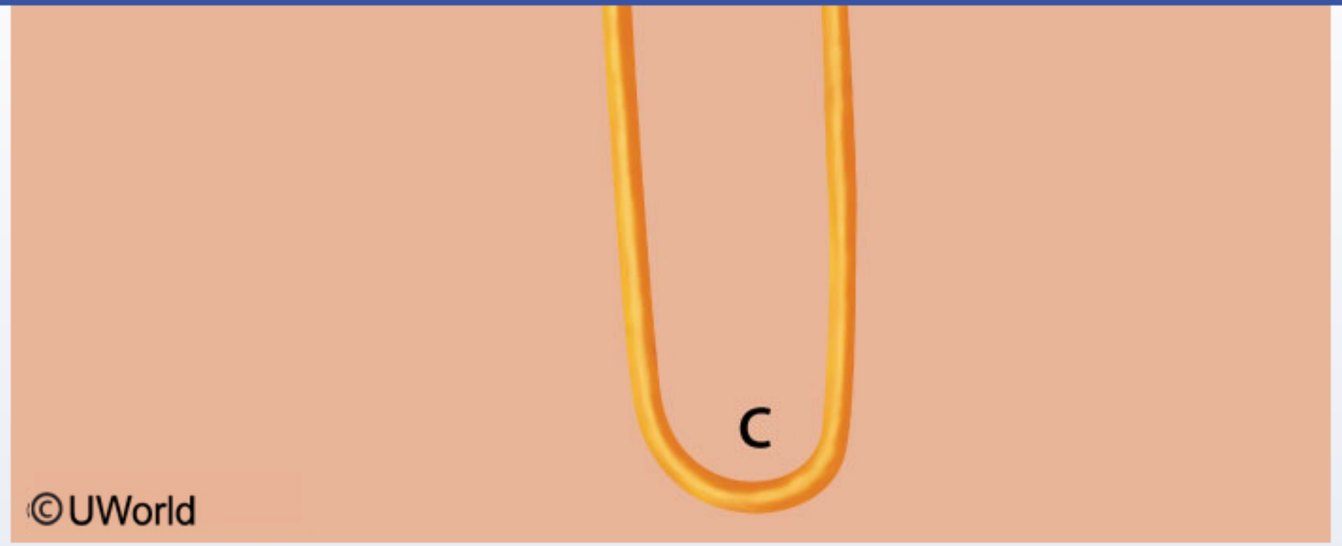

A. A (4%)
B. B (7%)
C. C (59%)
D. D (8%)
E. E (6%)
F. F (13%)

Omitted
Correct answer
C

59%
Answered correctly

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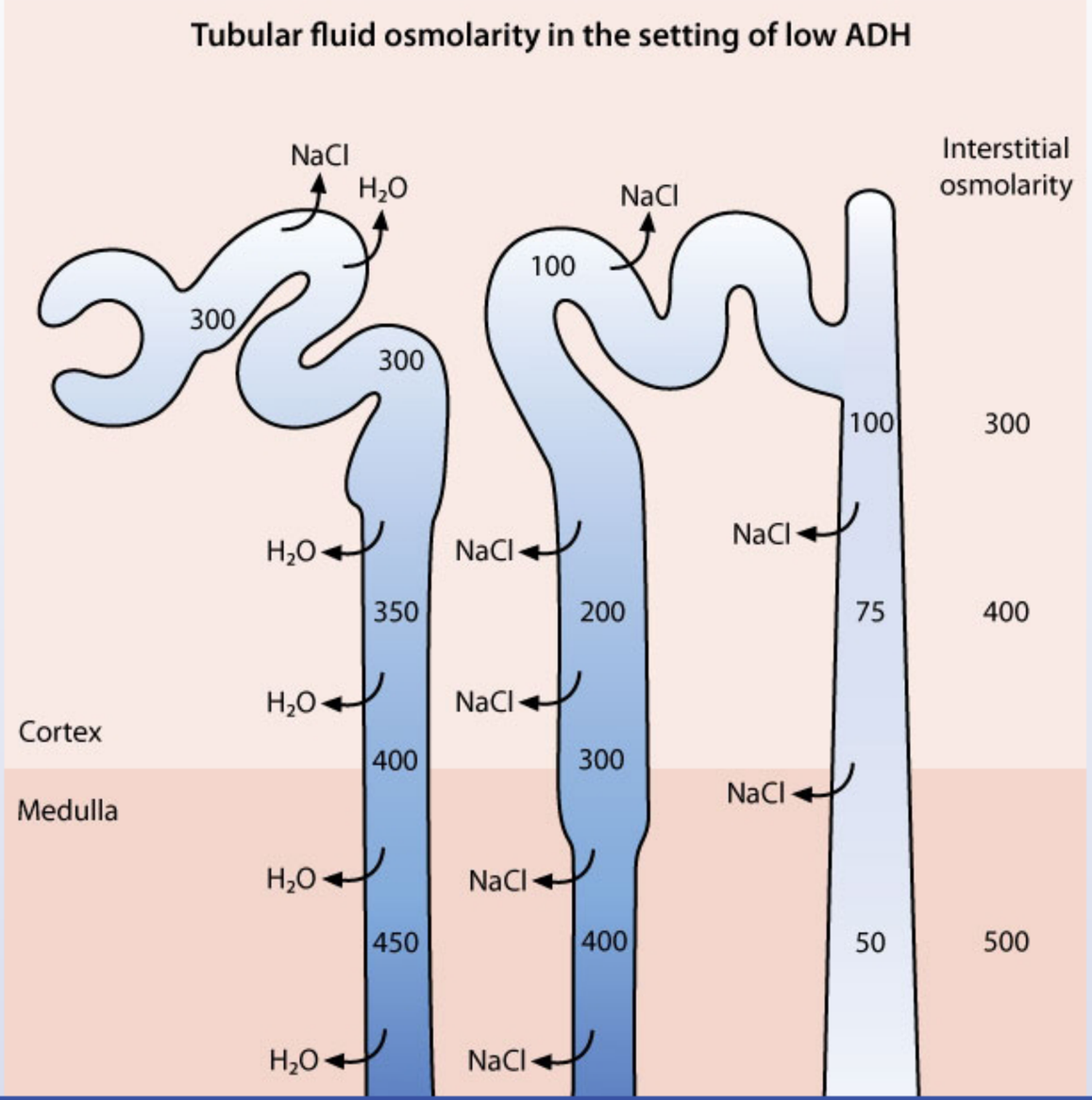
04/08/2020
Last Updated


Tubular fluid osmolarity in the setting of low ADH
NaCl
H_2O
NaCl
Interstitial osmolarity
300
300
100
100
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H_2O
NaCl
NaCl
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75
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Cortex
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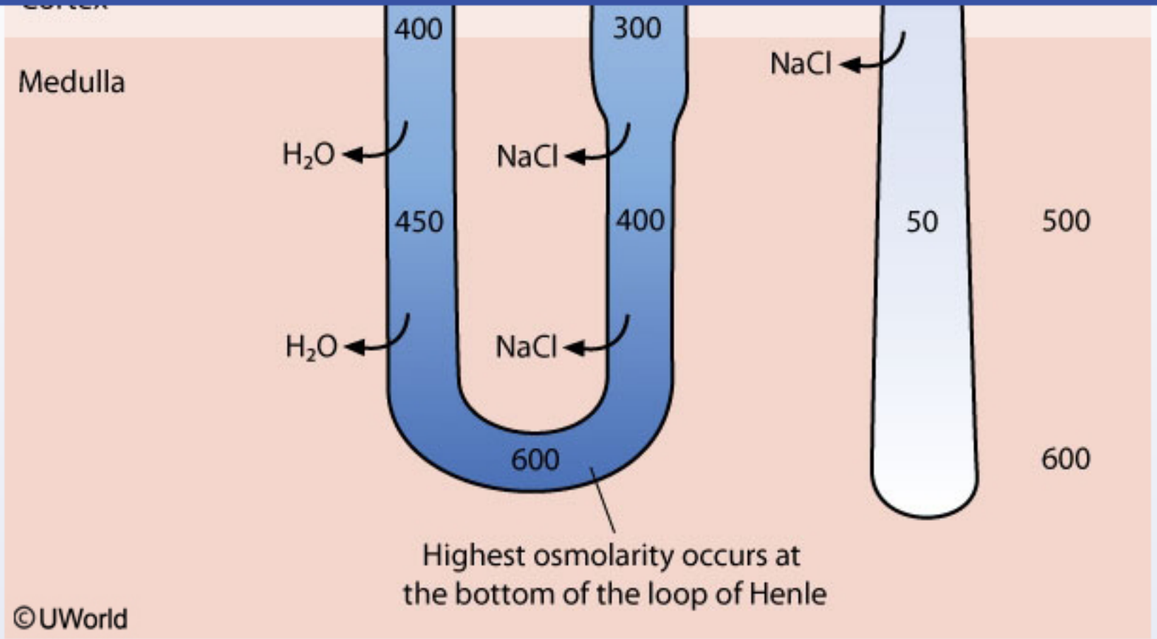

Tubular fluid osmolarity varies along the different segments of the nephron depending on each segment's permeability to water, the osmolarity of the renal interstitium, and the presence or absence of antidiuretic hormone (ADH):

1. In the proximal tubule, water is passively reabsorbed along with active transport of solutes into the interstitium. Fluid in the proximal tubule lumen is therefore isoosmotic with plasma **(Choice A)**.

2. The descending limb of the loop of Henle is permeable to water, but not solutes. As this segment of the nephron descends into the medullary interstitium, water moves down its concentration gradient from the lumen into the highly osmotic medulla. No reabsorption of electrolytes occurs in this segment, so the fluid in the lumen becomes hypertonic **(Choice B)**. However, tubular fluid will be the **most concentrated** at the **bottom of the loop** of Henle where interstitial osmolality is the greatest.

3. The thick ascending limb of the loop of Henle is impermeable to water. In this portion of the nephron, electrolytes are actively resorbed by the $Na^+/K^+/2Cl^-$ cotransporter, causing the osmolarity of the tubular fluid to decrease and become hypotonic **(Choice D)**.

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4. Reabsorption of solutes continues to occur in the distal convoluted tubule through the action of the NaCl symporter. Because the early distal convoluted tubule is impermeable to water, tubular fluid increases in hypotonicity in this segment of the nephron **(Choice E)**.

5. The water permeability of the collecting ducts depends on the presence of ADH. In the **absence of antidiuretic hormone** (ADH) (eg, overhydration, diabetes insipidus), the collecting ducts are impermeable to water, even when passing through high-osmolarity regions within the medullary concentration gradient. As solutes continue to be removed, tubular fluid in this segment can become as hypotonic as 50 mOsm/L, producing a very **dilute urine**.

(Choice F) When ADH levels are high (eg, dehydration), the collecting duct is highly permeable to water. Water leaves the tubular fluid driven by the high osmolarity of the medullary interstitium, and hypertonic urine is formed (up to 1200 mOsm/L). However, in this experiment the hypophysectomized animals are unable to produce ADH and will have dilute urine.

Educational objective:
Antidiuretic hormone (ADH) acts primarily on the collecting ducts, increasing their permeability to water. In the absence of ADH, the tubular fluid is most concentrated at the junction between the descending and ascending limbs of the loop of Henle and most dilute in the collecting ducts.

Physiology	Renal, Urinary Systems & Electrolytes	Nephron structure & physiology
Subject	System	Topic

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A 54-year-old missionary traveling alone in a remote region of Southern Asia becomes lost. After several days, he arrives at a small village. However, he has gone 24 hours without food or water, and his urine osmolarity is 1150 mOsm/L. The majority of the total amount of water filtered by this individual's glomeruli is reabsorbed in which of the following portions of the nephron?

A. Cortical collecting duct

B. Distal tubule

C. Loop of Henle

D. Medullary collecting duct

E. Proximal tubule

Submit

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A. Cortical collecting duct (16%)
B. Distal tubule (3%)
C. Loop of Henle (10%)
D. Medullary collecting duct (30%)
✓ E. Proximal tubule (38%)

Omitted
Correct answer
E

38%
Answered correctly

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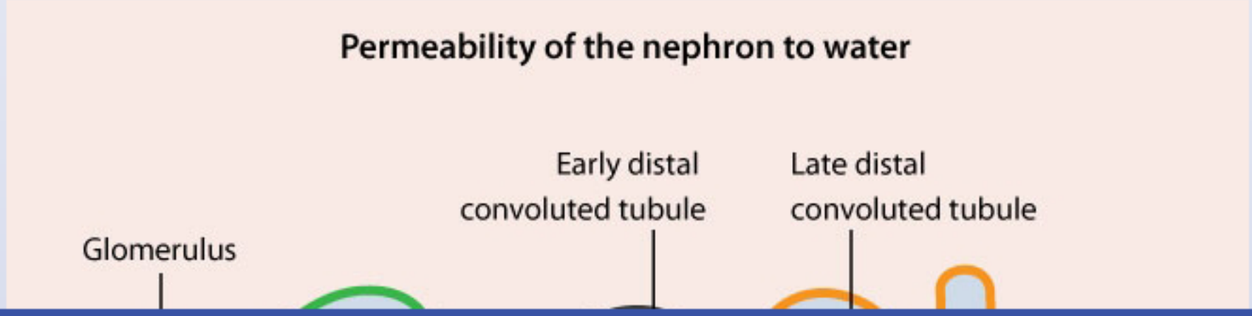
Time Spent

06/29/2020
Last Updated

Explanation



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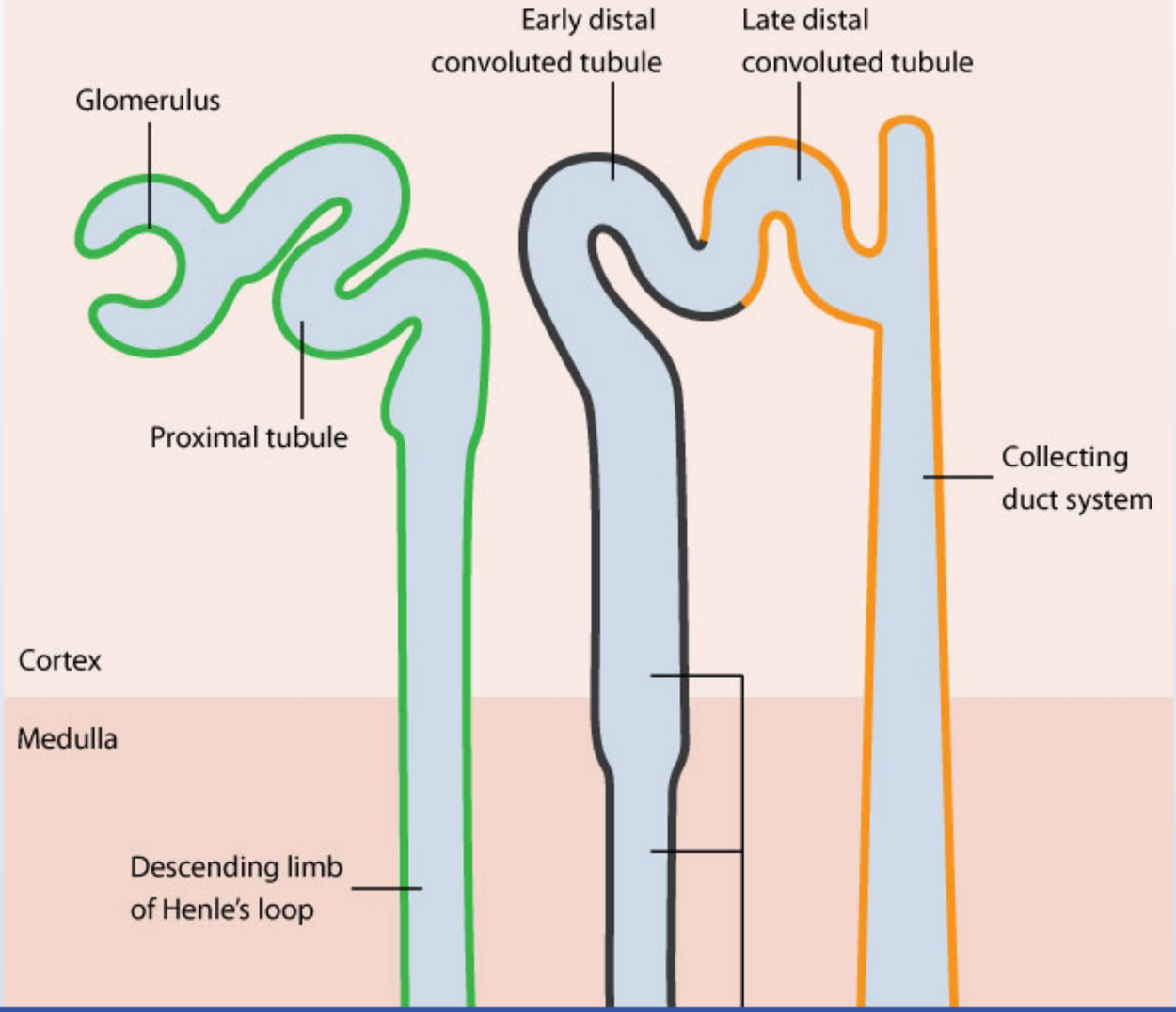
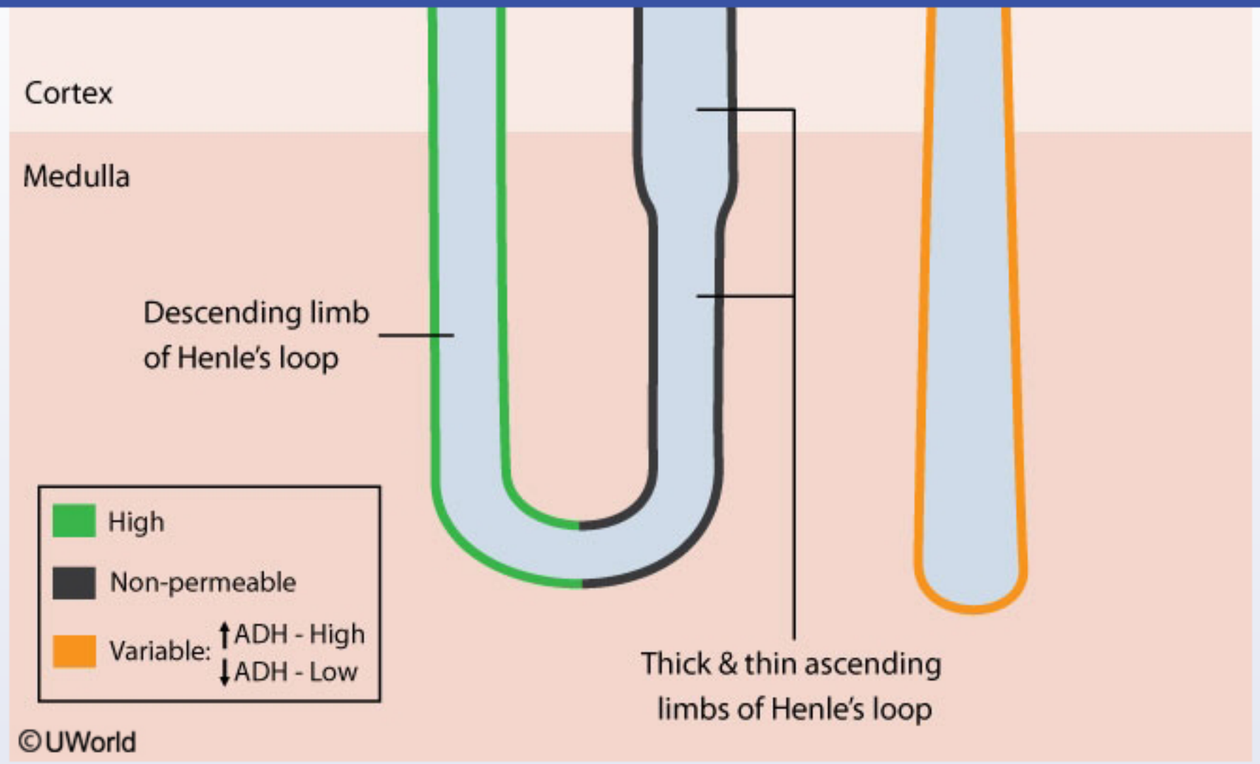
Permeability of the nephron to water





The **proximal tubules reabsorb >60%** of the water filtered by the glomeruli, regardless of the patient's hydration status. This water is reabsorbed isosmotically with solutes (eg, Na^+, Cl^-, glucose); no concentration or dilution of urine occurs in this segment.

In the dehydrated state, plasma osmolarity increases, stimulating osmoreceptors in the anterior hypothalamus. This triggers increased **antidiuretic hormone** (ADH) synthesis and release into the circulation. ADH then acts on the kidney to improve the water permeability of the collecting ducts, allowing production of maximally concentrated urine (osmolarity of 1200 mOsm/L). This increase in urine concentration with water deprivation reflects that the kidneys are functioning properly to conserve water. However, without eventual fluid replenishment, dehydration will ultimately progress to death because even at maximum resorptive capacity, the kidney still produces approximately 0.5 L of urine per day.

(Choice C) Urine concentration increases in the water-permeable descending loop of Henle due to the increasing osmolarity of the corticopapillary gradient in the renal interstitium; this segment normally reabsorbs about 20% of the filtered water volume.

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(Choices A, B, and D) In the dehydrated state, ADH promotes aquaporin (water channel) insertion into the apical membranes of the principal cells lining the late distal tubules and collecting ducts. Up to 20% of the original filtered volume of water can be reabsorbed here, allowing >99% of filtered water to be resorbed by the nephron during dehydration. No water is reabsorbed in these segments in the overhydrated state.

Educational objective:
Regardless of the patient's hydration status, the majority of water reabsorption in the nephron occurs in the proximal tubule passively with the reabsorption of solutes.

Physiology	Renal, Urinary Systems & Electrolytes	Hypovolemia
Subject	System	Topic

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A 58-year-old previously healthy woman comes to the emergency department due to left lower abdominal pain and fever. CT scan of the abdomen shows acute diverticulitis with microperforation. The patient is hospitalized and empiric antibiotics are begun. Food and fluids are withheld to promote bowel rest, and an isotonic saline infusion is administered for hydration. Over the next 2 days, the patient's fever and abdominal pain gradually improve, and pulse, blood pressure, and urine output remain within normal limits. Total administration of sodium chloride has been approximately 5 L. Compared with preadmission levels, which of the following changes have most likely occurred in this patient?

	Blood pH	Serum bicarbonate	Serum chloride	Urine sodium
A.	Decreased	Decreased	Decreased	Decreased
B.	Decreased	Decreased	Increased	Increased
C.	Decreased	Increased	Decreased	No change
D.	Increased	Increased	Decreased	Decreased
E.	Increased	Increased	Decreased	Increased

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	Blood pH	Serum bicarbonate	Serum chloride	Urine sodium
A. (5%)	Decreased	Decreased	Decreased	Decreased
✓ B. (50%)	Decreased	Decreased	Increased	Increased
C. (11%)	Decreased	Increased	Decreased	No change
D. (10%)	Increased	Increased	Decreased	Decreased
E. (21%)	Increased	Increased	Decreased	Increased

Omitted
Correct answer
B

50%
Answered correctly

02 secs
Time Spent

05/28/2020
Last Updated

Explanation

Explanation

Common causes of primary acid-base disturbance	
Metabolic acidosis	**Elevated anion gap** • Poor tissue perfusion (ie, lactic acidosis) • Diabetic ketoacidosis • Renal failure (ie, uremia) • Certain toxicities (eg, methanol, ethylene glycol) **Normal anion gap** • Severe diarrhea • Renal tubular acidosis • Excess normal saline infusion
Metabolic alkalosis	• Nasogastric suctioning or severe vomiting • Diuretic overuse • Primary hyperaldosteronism
Respiratory acidosis (hypoventilation)	• Central respiratory depression (eg, opioid overdose) • OHS, neuromuscular weakness • Chronic obstructive pulmonary disease
Respiratory alkalosis (hyperventilation)	• Acute V/Q mismatch (eg, PE, pneumonia) • Anxiety, inadequate pain control • High altitude, pregnancy

OHS = obesity hypoventilation syndrome; PE = pulmonary embolism; V/Q = ventilation/perfusion.

This patient likely has **nonanion gap metabolic acidosis** (NAGMA) due to **infusion of excess normal saline**. Excess sodium chloride increases serum chloride (Cl^-) to cause **hyperchloremia**. Because Cl^- and bicarbonate (HCO_3^-) are the predominant anions in the body, the increased serum Cl^- causes intracellular shifting of HCO_3^- to maintain electronegative balance. This "loss" of HCO_3^- **(reduced serum HCO_3^-)**

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Other causes of NAGMA usually involve loss of HCO_3^- from the kidneys (eg, renal tubular acidosis) or gastrointestinal tract (eg, severe diarrhea). With these etiologies, serum Cl^- is increased to compensate for the loss of HCO_3^-. Because of the inverse relationship between Cl^- and HCO_3^-, NAGMA of any etiology is also referred to as **hyperchloremic acidosis**.

(Choice A) Metabolic acidosis with hypochloremia (decreased serum HCO_3^-, pH, and serum Cl^-) can occur with diabetic ketoacidosis. The typical inverse relationship between serum HCO_3^- and Cl^- is disrupted due to the presence of unmeasured anions (ie, ketones) in the blood and profound Cl^- losses from osmotic diuresis (due to glucosuria). Urine Na^+ is low due to hypovolemia and consequent increased aldosterone-mediated urinary Na^+ reabsorption.

(Choice C) Increased serum HCO_3^- does not explain decreased pH (acidemia), but the combination of the two can occur with metabolic compensation for primary respiratory acidosis (eg, chronic hypoventilation). Serum Cl^- is decreased in response to the increase in serum HCO_3^-. Urine Na^+ is unchanged in the absence of a change in volume status.

(Choices D and E) Hypochloremic metabolic alkalosis (decreased serum Cl^-, increased serum HCO_3^- and pH) can occur in the setting of hypovolemia (eg, poor oral intake/vomiting, diuretic overuse) or hypervolemia (eg, primary hyperaldosteronism). Urine Na^+ is decreased with hypovolemic etiologies and increased with hypervolemic etiologies.

Educational objective:
The infusion of excessive normal saline (sodium chloride) is a common cause of nonanion gap metabolic acidosis. The excess intravascular chloride (Cl^-) causes intracellular shifting of bicarbonate (HCO_3^-) to reduce serum HCO_3^- and decrease blood pH.

References

- Hyperchloremic acidosis.

A 35-year-old woman comes to the office due to frequent urination. She describes drinking excessive amounts of water due to unquenchable thirst. She does not take any medications. Her blood glucose level is 86 mg/dL. A standard water deprivation test is performed. The results of urine osmolality during 4 hours of dehydration are presented in the table below. The patient's plasma osmolality after 3 hours of water deprivation was found to be 298 mOsm/L, and vasopressin was then administered subcutaneously.

Time (hours)	1	2	3	4
Urine osmolality (mOsm/L)	90	100	100	790

Which of the following is the most likely diagnosis in this patient?

A. Central diabetes insipidus
B. Complete nephrogenic diabetes insipidus
C. Partial nephrogenic diabetes insipidus
D. Post-obstructive polyuria
E. Primary polydipsia

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Time (hours)	1	2	3	4
Urine osmolality (mOsm/L)	90	100	100	790

Which of the following is the most likely diagnosis in this patient?

- A. Central diabetes insipidus (78%)
- B. Complete nephrogenic diabetes insipidus (5%)
- C. Partial nephrogenic diabetes insipidus (5%)
- D. Post-obstructive polyuria (0%)
- E. Primary polydipsia (9%)

Omitted
Correct answer
A

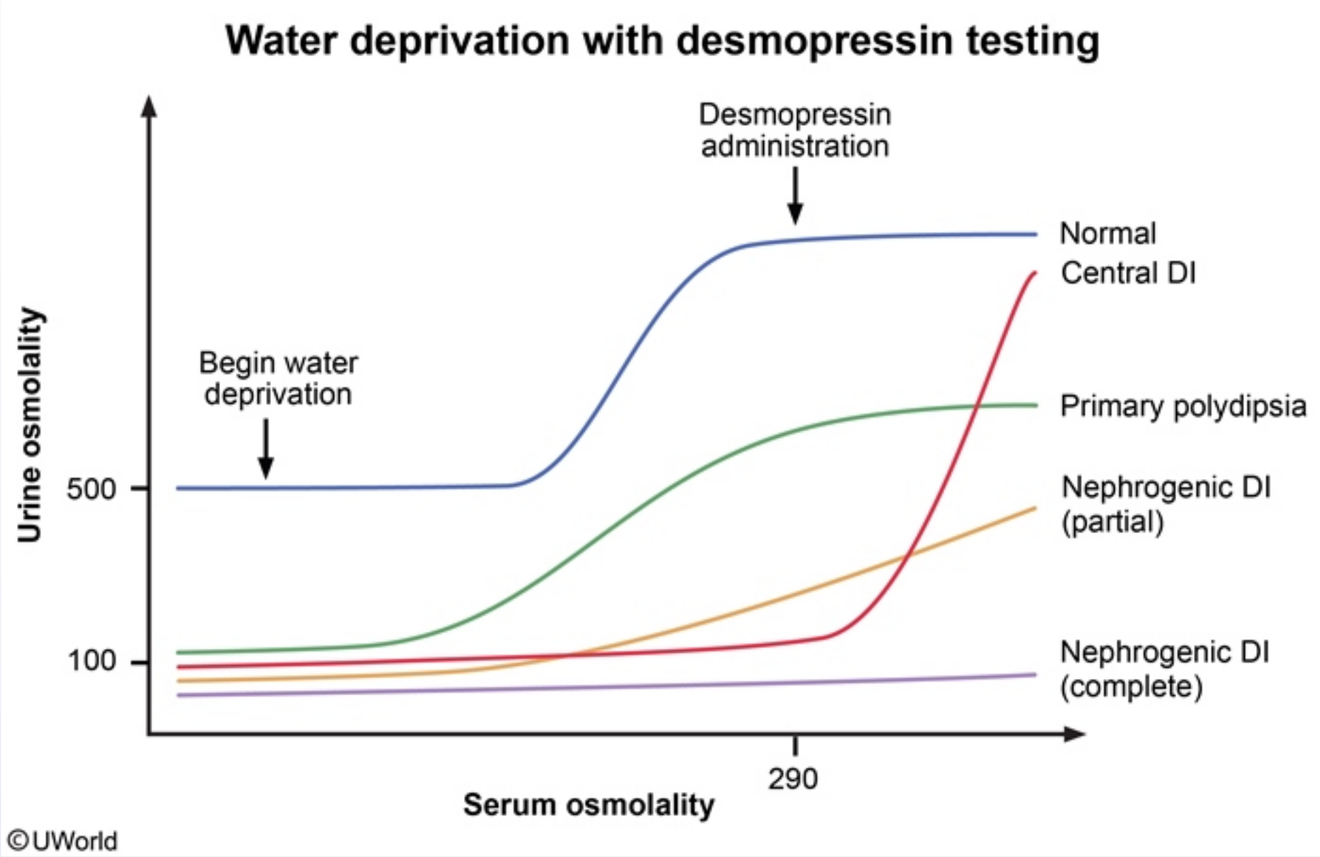
78%
Answered correctly

02 secs
Time Spent

04/18/2020
Last Updated

Explanation

Explanation



The collecting duct is impermeable to water in the absence of vasopressin (antidiuretic hormone [ADH]). ADH activates G protein-coupled V2 receptors on the basolateral tubular cell membrane, stimulating phosphorylation of intracellular proteins. This causes fusion of vesicles containing aquaporin 2 to the luminal membrane, where aquaporin serves as a water channel and allows water reabsorption in the collecting duct.

Diabetes insipidus (DI) is caused by either ADH deficiency (central DI) or complete/partial unresponsiveness of the kidneys to ADH (nephrogenic DI). The end result is free water loss in the urine with production of dilute urine (low specific gravity and urine osmolality) and dehydration that

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The collecting duct is impermeable to water in the absence of vasopressin (antidiuretic hormone [ADH]). ADH activates G protein-coupled V2 receptors on the basolateral tubular cell membrane, stimulating phosphorylation of intracellular proteins. This causes fusion of vesicles containing aquaporin 2 to the luminal membrane, where aquaporin serves as a water channel and allows water reabsorption in the collecting duct.

Diabetes insipidus (DI) is caused by either ADH deficiency (central DI) or complete/partial unresponsiveness of the kidneys to ADH (nephrogenic DI). The end result is free water loss in the urine with production of dilute urine (low specific gravity and urine osmolality) and dehydration that causes excessive thirst. A water deprivation test with desmopressin (DDAVP) administration can differentiate between central and nephrogenic DI. In patients with central DI and complete nephrogenic DI, the urine osmolality is persistently low despite an increase in serum osmolality with water deprivation. When desmopressin is administered, patients with central DI show a rapid increase in urine osmolality and reduction in urine volume, whereas those with complete nephrogenic DI do not **(Choice B).**

(Choice C) Patients with partial nephrogenic DI have a slow but steady rise in urine osmolality with increasing serum osmolality after water deprivation. There is no further increase in urine osmolality with DDAVP, and the urine osmolality remains low (<500 mOsm/L).

(Choice D) Relief of urinary obstruction (eg, Foley catheterization in patients with benign prostatic hyperplasia) may result in post-obstructive diuresis as the kidneys act to normalize fluid volume and solute levels. It is mostly seen in patients with a history of reduced urine output from chronic urinary obstruction. Urine osmolality remains within normal limits.

(Choice E) Patients with primary polydipsia exhibit an increase in serum and urine osmolality on water deprivation that is similar to partial nephrogenic DI. However, the correction in primary polydipsia is more rapid, and the urine osmolality returns to a level closer to normal (but still submaximal due to washout of the medullary osmotic gradient). A history of psychiatric disorders or medication-induced xerostomia is usually present.

Educational objective:
Patients with diabetes insipidus (DI) are unable to concentrate their urine in response to dehydration. Following desmopressin administration during the water deprivation test, urine osmolality increases to normal levels in central DI but does not change in complete nephrogenic DI.

References

- Diabetes insipidus.

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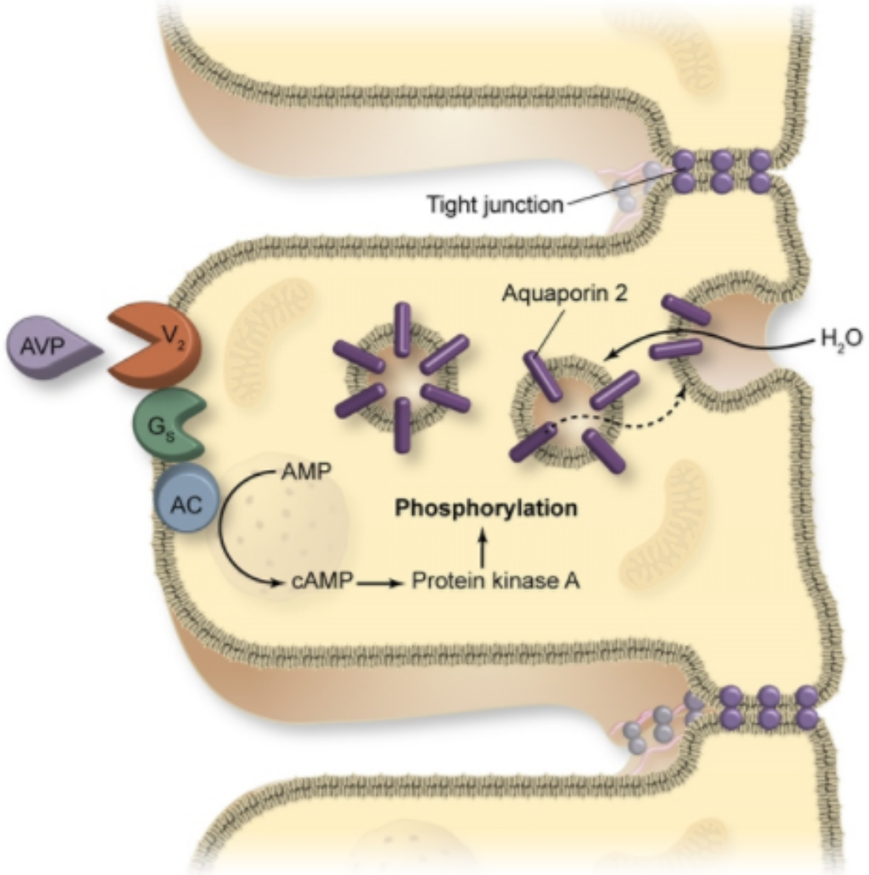
Exhibit Display

ADH action on collecting duct



AC = adenylyl cyclase; ADH = antidiuretic hormone; AVP = arginine vasopressin; cAMP = cyclic AMP.
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Exhibit Display

Causes of diabetes insipidus	
Central	• Pituitary tumors or resection • Head trauma • Primary brain tumors or infiltrative lesions (eg, sarcoidosis, lymphoma) • Brain metastases
Nephrogenic	• Drugs (eg, lithium, amphotericin B, gentamicin, cisplatin) • Hypercalcemia • Hypokalemia • Post obstructive diuresis

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Diabetes insipidus (DI) is caused by either ADH deficiency (central DI) or complete/partial unresponsiveness of the kidneys to ADH (nephrogenic DI). The end result is free water loss in the urine with production of dilute urine (low specific gravity and urine osmolality) and dehydration that causes excessive thirst. A water deprivation test with desmopressin (DDAVP) administration can differentiate between central and nephrogenic DI. In patients with central DI and complete nephrogenic DI, the urine osmolality is persistently low despite an increase in serum osmolality with water deprivation. When desmopressin is administered, patients with central DI show a rapid increase in urine osmolality and reduction in urine volume, whereas those with complete nephrogenic DI do not **(Choice B).**

(Choice C) Patients with partial nephrogenic DI have a slow but steady rise in urine osmolality with increasing serum osmolality after water deprivation. There is no further increase in urine osmolality with DDAVP, and the urine osmolality remains low (<500 mOsm/L).

(Choice D) Relief of urinary obstruction (eg, Foley catheterization in patients with benign prostatic hyperplasia) may result in post-obstructive diuresis as the kidneys act to normalize fluid volume and solute levels. It is mostly seen in patients with a history of reduced urine output from chronic urinary obstruction. Urine osmolality remains within normal limits.

(Choice E) Patients with primary polydipsia exhibit an increase in serum and urine osmolality on water deprivation that is similar to partial nephrogenic DI. However, the correction in primary polydipsia is more rapid, and the urine osmolality returns to a level closer to normal (but still submaximal due to washout of the medullary osmotic gradient). A history of psychiatric disorders or medication-induced xerostomia is usually present.

Educational objective:
Patients with diabetes insipidus (DI) are unable to concentrate their urine in response to dehydration. Following desmopressin administration during the water deprivation test, urine osmolality increases to normal levels in central DI but does not change in complete nephrogenic DI.

References

- Diabetes insipidus.

Physiology	Renal, Urinary Systems & Electrolytes	Diabetes insipidus
Subject	System	Topic

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A group of researchers is studying secondary hypertension in porcine models of renal artery stenosis. During an experiment, a clip is placed that constricts the right renal artery to 30% of its original cross-sectional area. A few days later, hemodynamic and biochemical measurements are recorded and compared to measurements obtained before clip placement. Which of the following changes is most likely to be seen in the experimental animals?

A. Decreased inferior vena cava aldosterone level

B. Decreased systemic vascular resistance

C. Increased glomerular filtration in the right kidney

D. Increased renin production in the left kidney

E. Increased sodium excretion in the left kidney

Submit

A group of researchers is studying secondary hypertension in porcine models of renal artery stenosis. During an experiment, a clip is placed that constricts the right renal artery to 30% of its original cross-sectional area. A few days later, hemodynamic and biochemical measurements are recorded and compared to measurements obtained before clip placement. Which of the following changes is most likely to be seen in the experimental animals?

- A. Decreased inferior vena cava aldosterone level (2%)
- B. Decreased systemic vascular resistance (5%)
- C. Increased glomerular filtration in the right kidney (26%)
- D. Increased renin production in the left kidney (31%)
- ✓ E. Increased sodium excretion in the left kidney (33%)

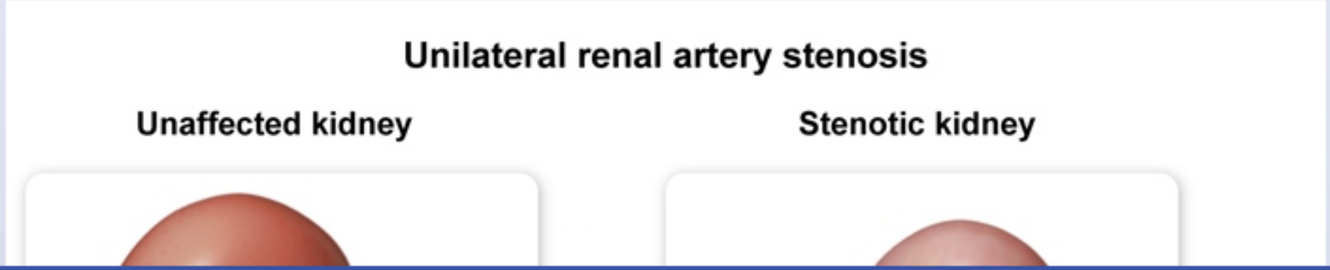
Omitted
Correct answer
E

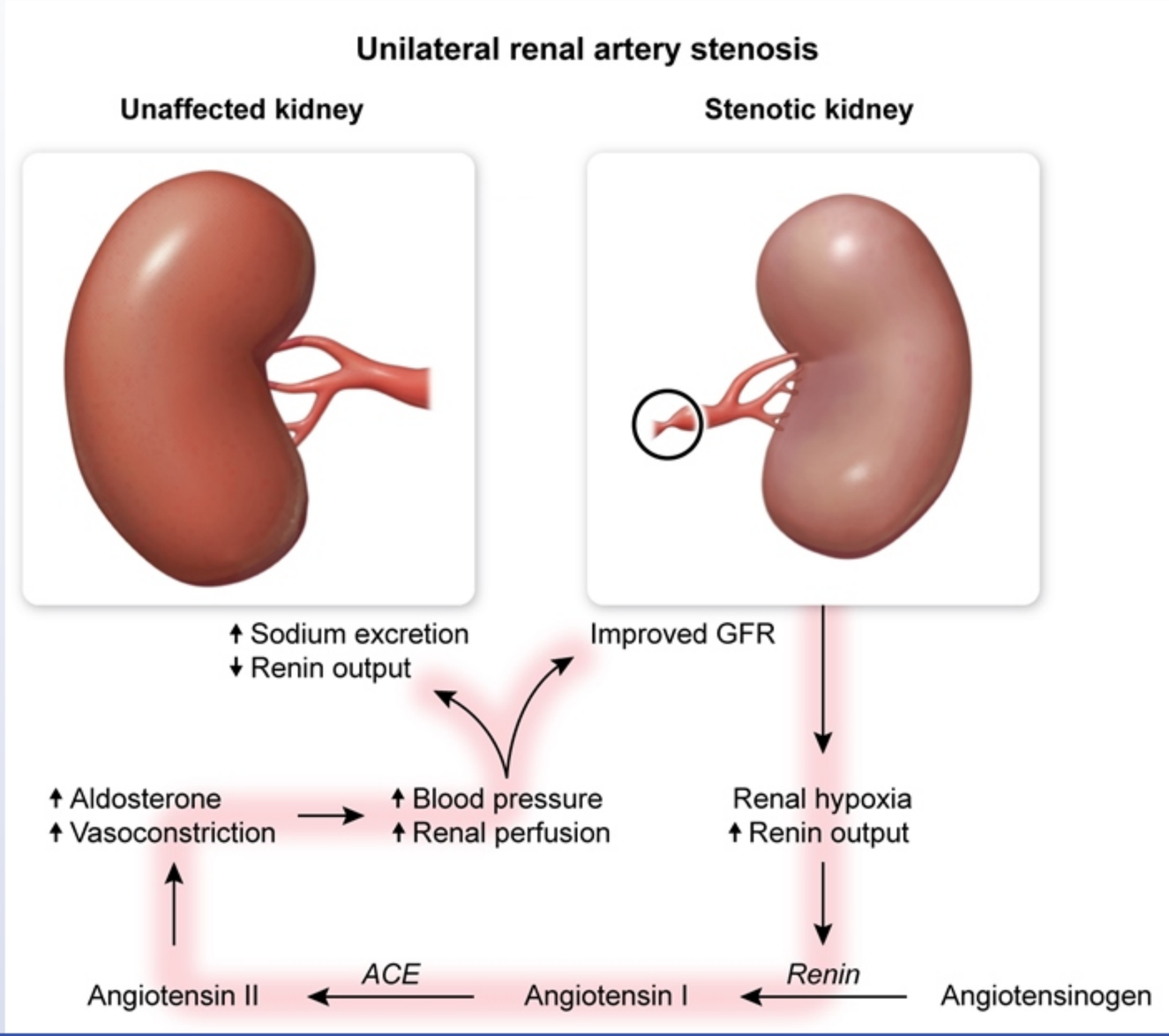
33%
Answered correctly

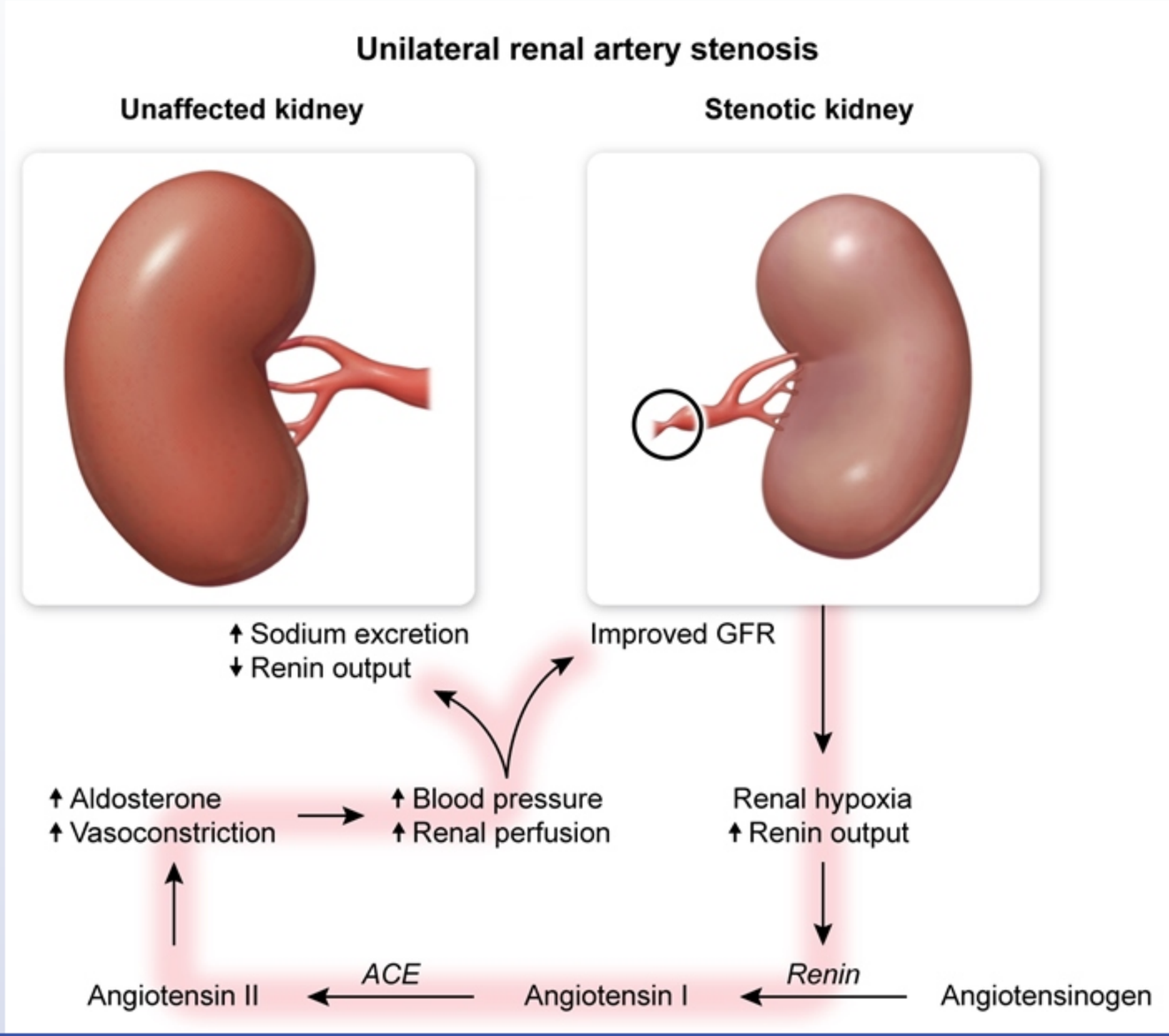
02 secs
Time Spent

04/16/2020
Last Updated

Explanation




Unilateral renal artery stenosis
Unaffected kidney
Stenotic kidney
↑ Sodium excretion
↓ Renin output
Improved GFR
↑ Aldosterone
↑ Vasoconstriction
↑ Blood pressure
↑ Renal perfusion
Renal hypoxia
↑ Renin output
Angiotensin II
ACE
Angiotensin I
Renin
Angiotensinogen


Unilateral renal artery stenosis
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↑ Blood pressure
↑ Renal perfusion
Renal hypoxia
↑ Renin output
Angiotensin II
ACE
Angiotensin I
Renin
Angiotensinogen

Unilateral renal hypoperfusion (due to **renal artery stenosis** or clipping) causes activation of the **renin-angiotensin-aldosterone system** (RAAS). In response to low perfusion pressures, the juxtaglomerular cells of the kidney synthesize renin, which converts angiotensinogen (synthesized in the liver) to angiotensin I. Angiotensin-converting enzyme, which is synthesized largely in the lungs, then converts angiotensin I to its active form, angiotensin II.

Angiotensin II has multiple actions to increase systemic blood pressure. It directly **increases systemic vascular** resistance through generalized arteriolar vasoconstriction **(Choice B)**. It also increases sodium and water reabsorption both directly, by increasing sodium reabsorption in the proximal tubule, and indirectly, by stimulating **aldosterone** synthesis in the adrenal cortex and antidiuretic hormone in the hypothalamus **(Choice A)**. Elevated systemic pressure and blood volume help overcome the decreased perfusion pressures in the stenotic kidney and maintain a near-normal filtration rate.

However, the **unaffected kidney** is exposed to elevated systemic pressures, resulting in **increased sodium excretion** due to a pressure natriuresis effect. Although this helps reduce circulating volume, many patients with renal artery stenosis have **chronic hypertension** due to persistent hyperreninemia and angiotensin II–induced vasoconstriction caused by the stenotic kidney.

(Choice C) After placement of the clip, glomerular filtration rate will drop in the stenotic kidney, triggering compensatory RAAS activation. This increases the perfusion pressure of the stenotic kidney, helping to normalize glomerular filtration rate. However, like most compensatory responses, the increase in filtration caused by RAAS activation is not enough to overcome the initial drop in filtration caused by clip placement. Therefore, the filtration rate remains less than normal in the stenotic kidney.

(Choice D) Renin production is suppressed in the unaffected kidney due to its exposure to elevated systemic pressures.

Educational objective:
Unilateral renal artery stenosis causes hypoperfusion and activation of the renin-angiotensin-aldosterone system. Angiotensin II causes arteriolar vasoconstriction and increases aldosterone and antidiuretic hormone synthesis. The resultant hypertension helps reduce the decline in glomerular filtration rate in the affected kidney, but causes a pressure natriuresis with increased sodium excretion in the unaffected kidney.

Physiology	Renal, Urinary Systems & Electrolytes	Renal artery stenosis
Subject	System	Topic

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Physiologists are investigating renal autoregulatory mechanisms in an animal species that closely mimics human physiology. During one of their experiments, renal blood flow and glomerular filtration rate are measured in an anesthetized animal in response to changes in mean arterial pressure. The data they obtain is shown on the graph below.

Assuming a hematocrit of 0.50, what is the best estimate of the filtration fraction when the mean arterial pressure is 120 mm Hg?

A. 0.1
B. 0.2
C. 0.4
D. 0.5
E. 0.9

Submit

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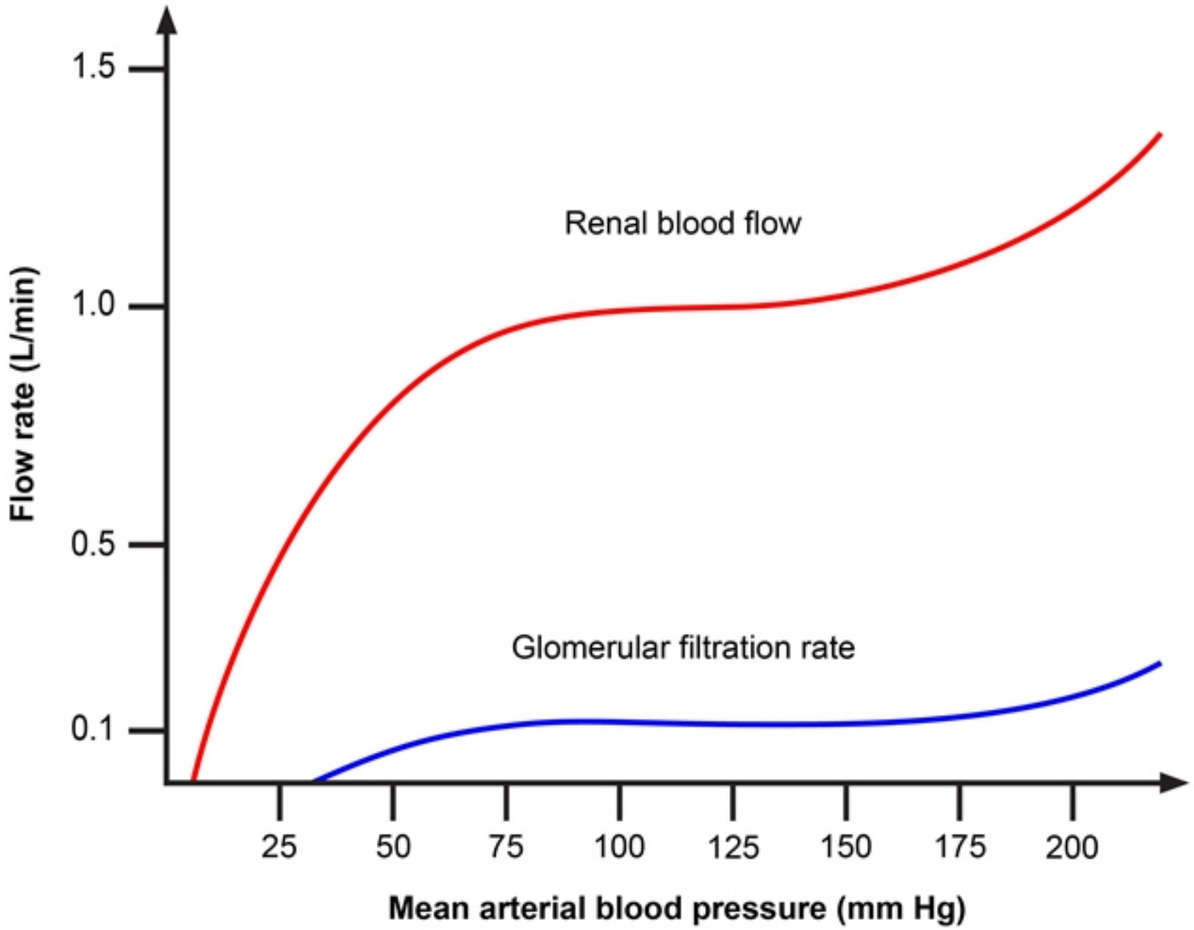

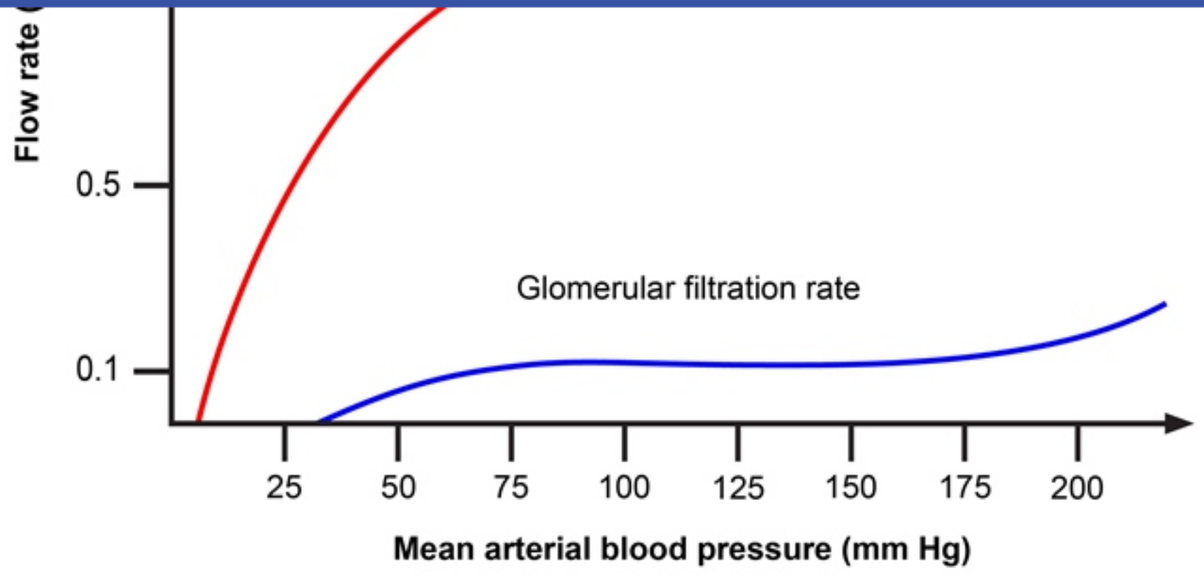

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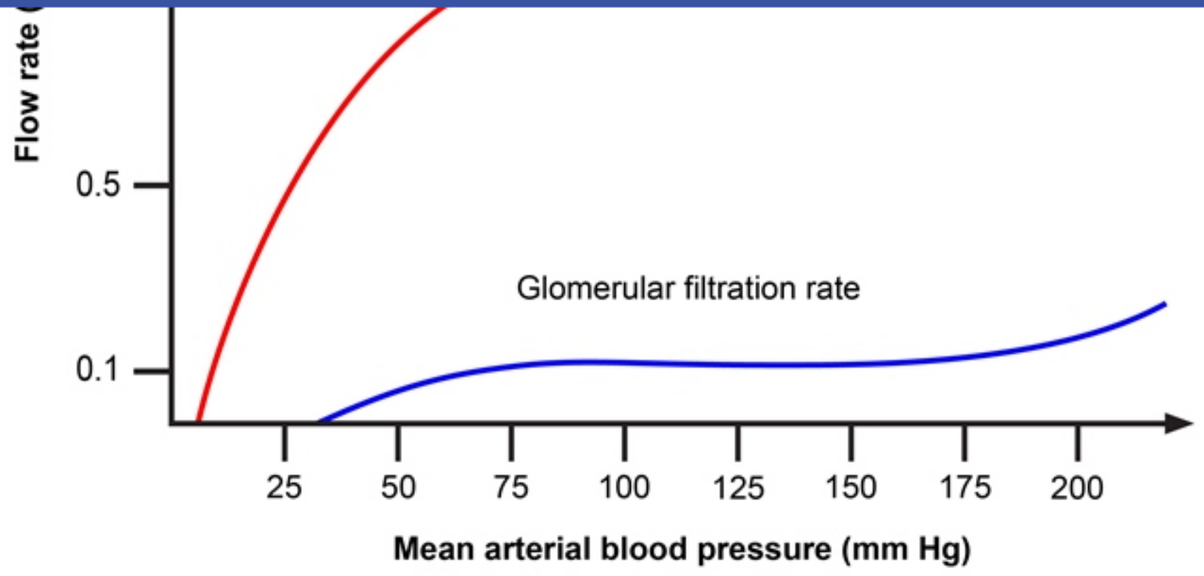
Assuming a hematocrit of 0.50, what is the best estimate of the filtration fraction when the mean arterial pressure is 120 mm Hg?

- A. 0.1
- B. 0.2
- C. 0.4
- D. 0.5
- E. 0.9

Submit



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Assuming a hematocrit of 0.50, what is the best estimate of the filtration fraction when the mean arterial pressure is 120 mm Hg?

- A. 0.1 (31%)
- ✓ B. 0.2 (47%)
- C. 0.4 (5%)
- D. 0.5 (11%)
- E. 0.9 (3%)

Omitted
Correct answer

47%
Answered correctly

05 secs
Time Spent

03/24/2020
Last Updated

Explanation

The **filtration fraction (FF)** is the fraction of **plasma** flowing through the glomeruli that is filtered across the glomerular capillaries into Bowman's space. It can be thought of as the ratio between the glomerular filtration rate (GFR) and renal plasma flow (RPF):

FF = GFR/RPF

RPF is used to calculate FF rather than renal blood flow (RBF) because RBF includes the volume of the blood that is occupied by erythrocytes, a volume unavailable for filtration across the glomerular capillaries. The RPF quantifies the volume of plasma that is able to pass through the glomerular capillaries more accurately and can be calculated from the RBF using the following equation:

RPF = RBF * (1 - Hematocrit)

In this case, at a mean arterial pressure of 120 mm Hg, the experimental animal has a RBF of 1.0 L/min and a GFR of 0.1 L/min. Because the hematocrit is 0.5, this gives:

RPF = (1.0 L/min) * (1 - 0.5) = 0.5 L/min

Therefore, FF = (0.1 L/min) / (0.5 L/min) = 0.2.

Educational objective:
The filtration fraction is the fraction of plasma flowing through the glomeruli that is filtered across the glomerular capillaries into Bowman's space (FF = GFR/RPF). Renal plasma flow can be determined from renal blood flow by multiplying the renal blood flow by (1 – Hematocrit).

Physiology	Renal, Urinary Systems & Electrolytes	Drug metabolism and clearance
Subject	System	Topic

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A 56-year-old man with chronic renal insufficiency due to polycystic kidney disease is evaluated for placement of an arteriovenous fistula for dialysis access. Blood pressure is 140/90 mm Hg and pulse is 80/min. Examination shows 2+ bilateral edema of the lower extremities. Estimated glomerular filtration rate is 15 mL/min/1.73 m^2. Which of the following sets of laboratory findings is most likely in this patient?

	Parathyroid hormone	Serum calcium	Serum phosphorus	25-hydroxyvitamin D	1,25-dihydroxyvitamin D
A.	↑	↓	↑	Normal	↓
B.	↑	↑	↓	Normal	↑
C.	↓	↓	↑	Normal	↓
D.	↑	↓	↓	↓	↓
E.	↓	↑	↑	Normal	↑

Submit

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	Parathyroid hormone	Serum calcium	Serum phosphorus	25-hydroxyvitamin D	1,25-dihydroxyvitamin D
✓ A. (83%)	↑	↓	↑	Normal	↓
B. (3%)	↑	↑	↓	Normal	↑
C. (4%)	↓	↓	↑	Normal	↓
D. (7%)	↑	↓	↓	↓	↓
E. (1%)	↓	↑	↑	Normal	↑

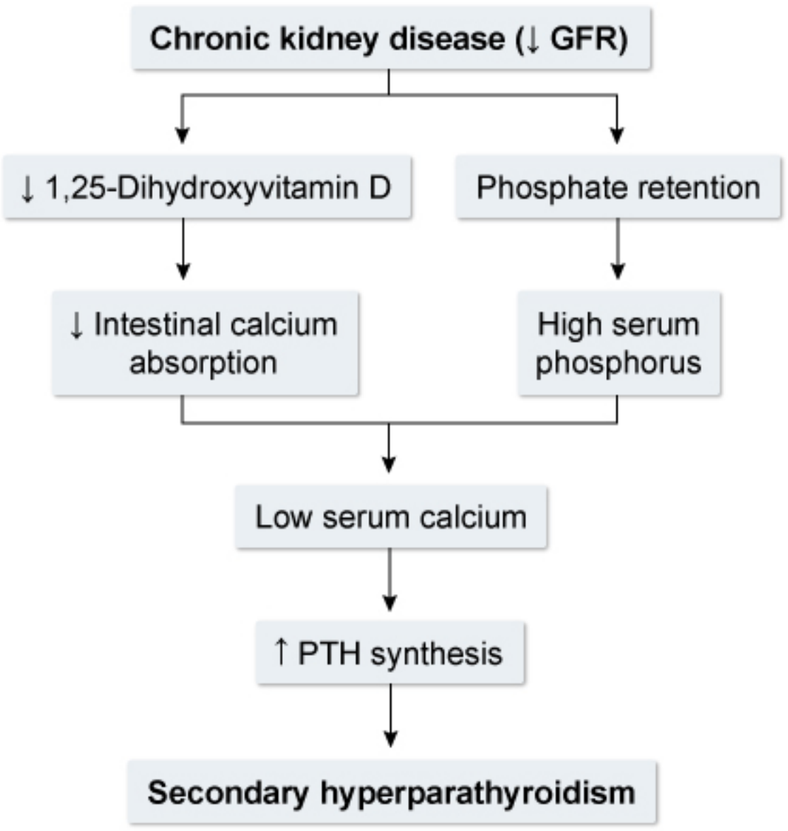
Omitted
Correct answer
A

83%
Answered correctly

02 secs
Time Spent

02/05/2020
Last Updated

Explanation



GFR = glomerular filtration rate; **PTH** = parathyroid hormone.

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This patient has advanced **chronic kidney disease** (CKD). CKD can cause **hyperphosphatemia** due to the impaired ability of the kidneys to excrete phosphorus (particularly when GFR is <20 mL/min/1.73 m^2). Elevated blood phosphate triggers the release of fibroblast growth factor 23 from bone, which **lowers calcitriol** (1,25-dihydroxyvitamin D) production and intestinal calcium absorption. In addition, patients with advanced CKD typically have decreased renal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (the more active form) because of inadequate

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(Choice B) Primary hyperparathyroidism is characterized by hypercalcemia, hypophosphatemia (due to increased renal excretion of phosphorus), and increased renal production of 1,25-dihydroxyvitamin D. In secondary hyperparathyroidism due to CKD, PTH is high but serum phosphate is elevated and hypercalcemia would not be seen.

(Choice C) Hypoparathyroidism is characterized by hypocalcemia, hyperphosphatemia, and decreased renal production of 1,25-dihydroxyvitamin D. Hypoparathyroidism is usually caused by autoimmune disease or iatrogenic injury to the parathyroid glands during neck surgery.

(Choice D) Vitamin D deficiency (ie, low 25-hydroxyvitamin D) causes decreased absorption of dietary calcium and leads to hypocalcemia. The resulting increase in PTH (secondary hyperparathyroidism) causes decreased renal reabsorption of phosphate, leading to hypophosphatemia. 1,25-Dihydroxyvitamin D levels are typically low, although the increased renal conversion due to PTH may restore levels to within laboratory norms.

(Choice E) Elevated 1,25-dihydroxyvitamin D levels can be seen in granulomatous diseases (eg, sarcoidosis) and in excess intake of calcitriol supplements, and lead to increased intestinal absorption of calcium and phosphate (with hypercalcemia and hyperphosphatemia) and suppression of PTH.

Educational objective:
Chronic kidney disease can cause hyperphosphatemia due to impaired renal excretion of phosphorus. Elevated blood phosphate triggers the release of fibroblast growth factor 23, which lowers calcitriol production and intestinal calcium absorption. The resulting hypocalcemia, along with hyperphosphatemia, leads to secondary hyperparathyroidism.

References

- Diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder: synopsis of the Kidney Disease: Improving Global Outcomes 2017 clinical practice guideline update

leads to **secondary hyperparathyroidism**.

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Chronic kidney disease can cause hyperphosphatemia due to impaired renal excretion of phosphorus. Elevated blood phosphate triggers the release of fibroblast growth factor 23, which lowers calcitriol production and intestinal calcium absorption. The resulting hypocalcemia, along with hyperphosphatemia, leads to secondary hyperparathyroidism.

References

- Diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder: synopsis of the Kidney Disease: Improving Global Outcomes 2017 clinical practice guideline update.

Physiology	Renal, Urinary Systems & Electrolytes	Chronic kidney disease
Subject	System	Topic

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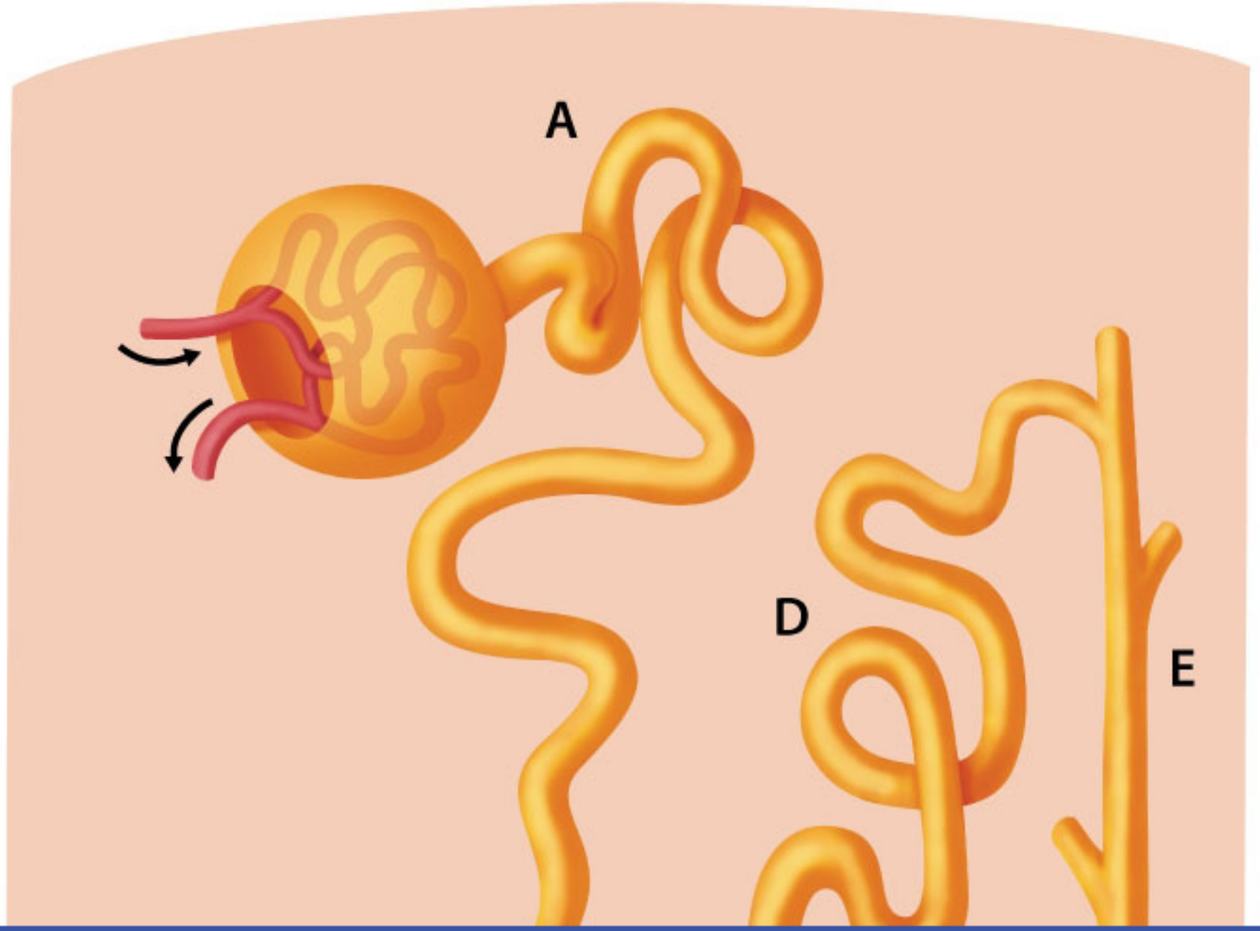
Renal physiologists are studying how hydration status affects the mechanisms of urine concentration and dilution in humans. To do this, they developed a technique in experimental animals that permits sampling of tubular fluid in different parts of the nephron. A tubular fluid sample with an osmolarity of 110 mOsm/L is obtained from a healthy animal after 12 hours of water deprivation. Assuming the physiology of this animal mirrors human physiology, which of the following sites along the nephron was most likely sampled?



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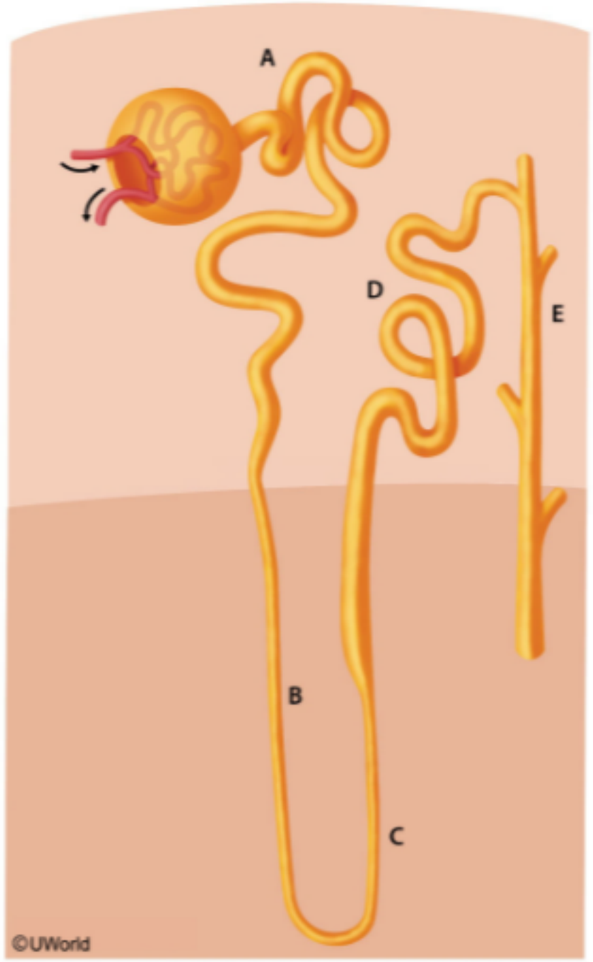

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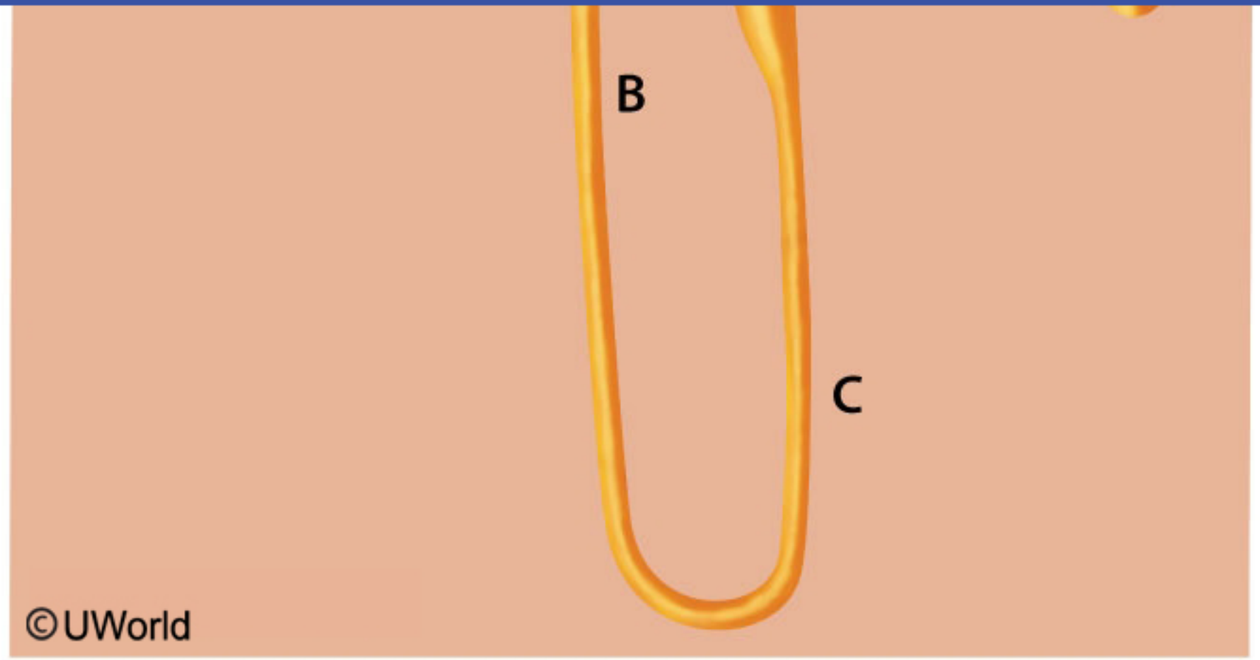


A. A

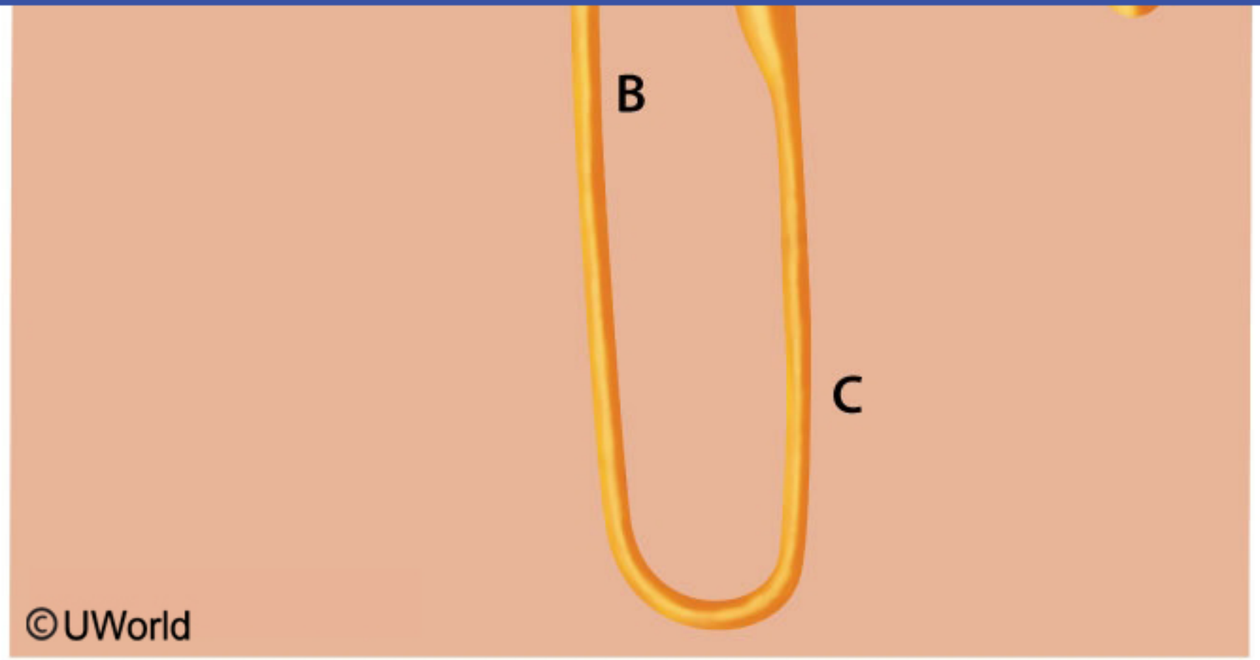
B. B

C. C

D. D

E. E

Submit



A. A (17%)
B. B (9%)
C. C (10%)
✓ D. D (45%)
E. E (16%)

Omitted
Correct answer

45%
Answered correctly

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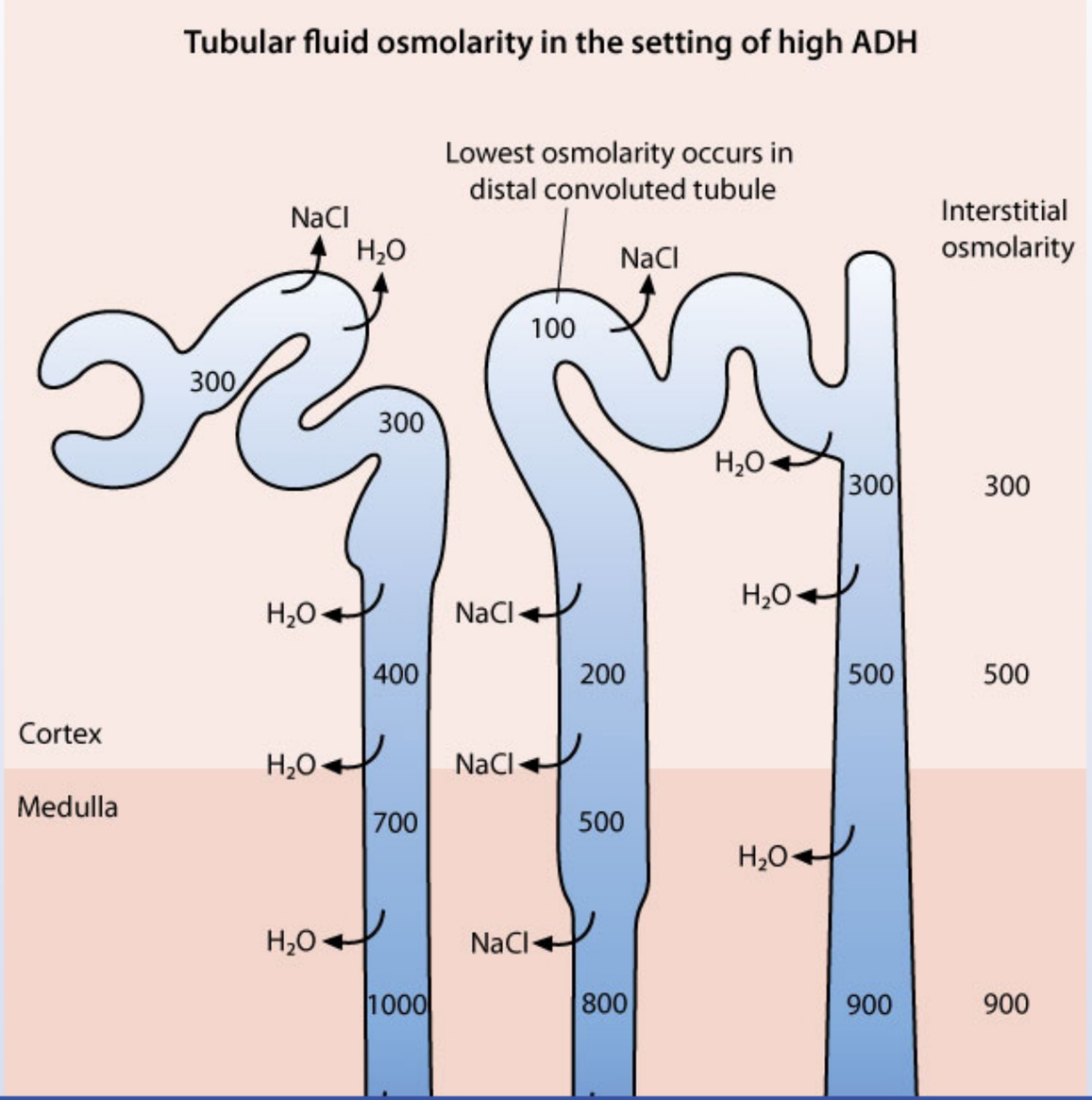
Time Spent

04/08/2020
Last Updated


Tubular fluid osmolarity in the setting of high ADH
Lowest osmolarity occurs in distal convoluted tubule
Interstitial osmolarity
NaCl
H_2O
300
300
100
NaCl
H_2O
300
300
H_2O
NaCl
400
200
H_2O
500
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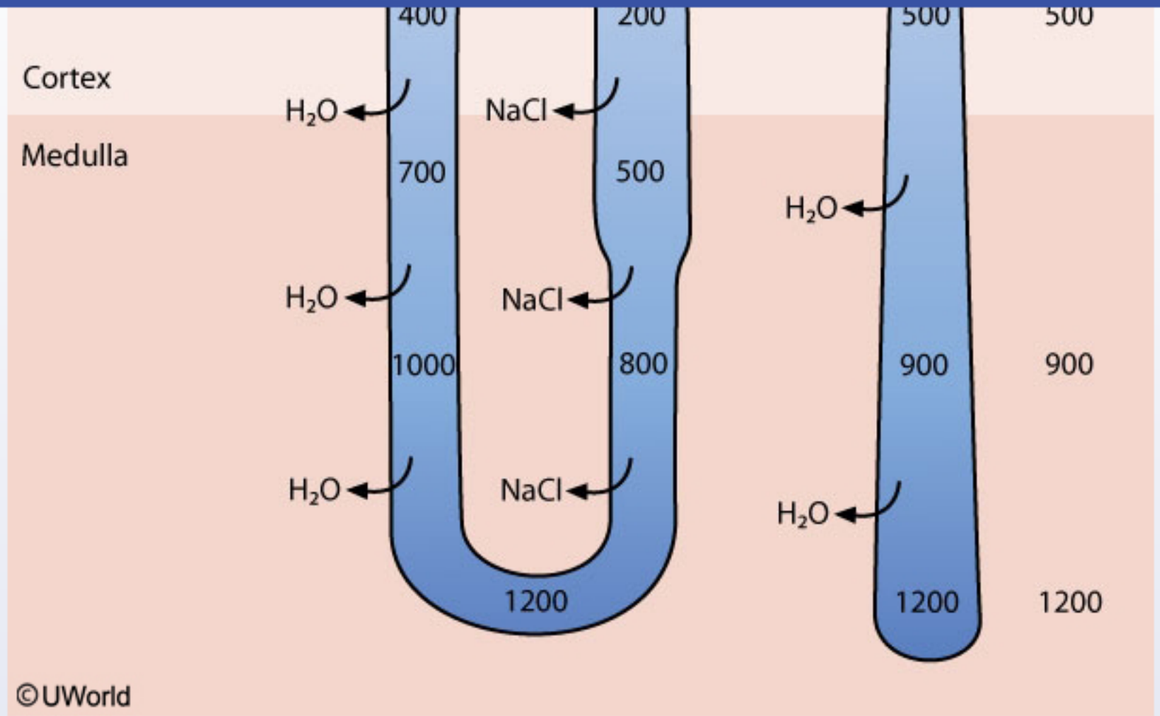

Water deprivation results in **antidiuretic hormone (ADH)** release from the posterior pituitary gland. This hormone stimulates V2 receptors on principal cells in the renal collecting ducts, causing translocation of aquaporin 2 channels into the apical cell membrane. Aquaporin 2 is a water channel that spans the luminal membrane, enhancing the water permeability of the principal cells. In the presence of **high ADH**, the tubular fluid osmolarity follows this pattern:

1. In the proximal tubule, water is reabsorbed along with electrolytes. The tubular fluid in this segment remains isotonic with plasma (300 mOsm/L) whether the final urine is concentrated or diluted **(Choice A)**.
2. In the descending limb of the loop of Henle, free water is drawn out of the tubules into the renal interstitium and the tubular fluid becomes hypertonic (> 300 mOsm/L, typically reaching 1200 mOsm/L when ADH levels are high) **(Choice B)**.
3. The thick and thin ascending limbs of the loop of Henle are the primary region of urine dilution. These regions are impermeable to water; electrolytes such as NaCl are passively reabsorbed in the thin ascending limb **(Choice C)** and actively reabsorbed in the thick ascending

principal cells in the renal collecting ducts, causing translocation of aquaporin 2 channels into the apical cell membrane. Aquaporin 2 is a water channel that spans the luminal membrane, enhancing the water permeability of the principal cells. In the presence of **high ADH**, the tubular fluid osmolarity follows this pattern:

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3. The thick and thin ascending limbs of the loop of Henle are the primary region of urine dilution. These regions are impermeable to water; electrolytes such as NaCl are passively reabsorbed in the thin ascending limb **(Choice C)** and actively reabsorbed in the thick ascending limb. The tubular fluid becomes increasing hypotonic (< 300 mOsm/L) within this region.
4. The **distal convoluted tubule** is relatively impermeable to water, so the tubular fluid remains hypotonic. Reabsorption of solutes continues to occur; thus, fluid in the distal tubules is the **most dilute** (lowest osmolarity, approaching 100 mOsm/L).
5. In the presence of ADH, the collecting duct is highly permeable to water. Water leaves the tubular fluid driven by the high osmolarity of the medullary interstitium, and **hypertonic urine** is formed (up to 1200 mOsm/L). The collecting duct system is the primary region of urine concentration through the mechanism of ADH-mediated water absorption.

(Choice E) In contrast, when ADH levels are low, the collecting duct remains impermeable to water. Thus, tubular fluid in this segment can become as hypotonic as 50 mOsm/L while solutes continue to be removed. However, in this case ADH levels are high, so the distal convoluted tubule will be the region of lowest osmolality.

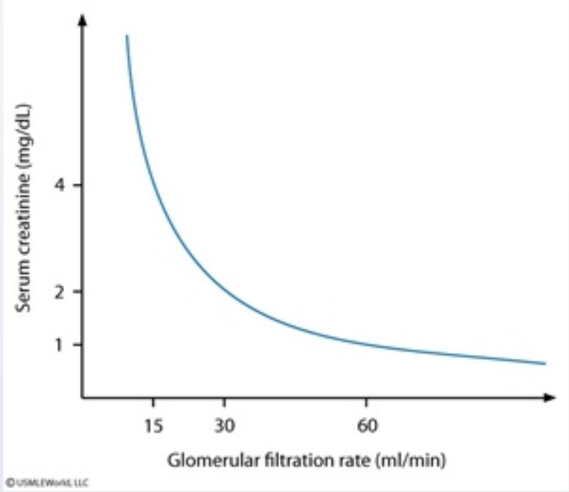
Educational objective:
Dehydration stimulates ADH secretion. ADH acts on the collecting ducts, increasing their permeability to water. Thus, in the presence of ADH, the collecting ducts contain the most concentrated fluid in the nephron, while the distal convoluted tubule contains the most dilute fluid.

References

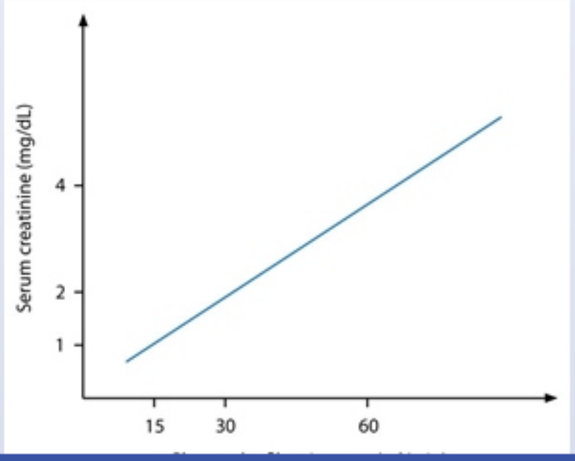
- The physiology of urinary concentration: an update.

A 65-year-old man with type 2 diabetes mellitus comes to the physician for a routine follow-up appointment. He was started on oral hypoglycemic medications 12 years ago but was recently switched to long-acting insulin due to inadequate blood sugar control. His last serum creatinine level was 2.1 mg/dL. The patient is concerned about his elevated creatinine level and how it relates to his kidney function. Which of the following graphs most accurately represents the relationship between serum creatinine and glomerular filtration rate?

A.

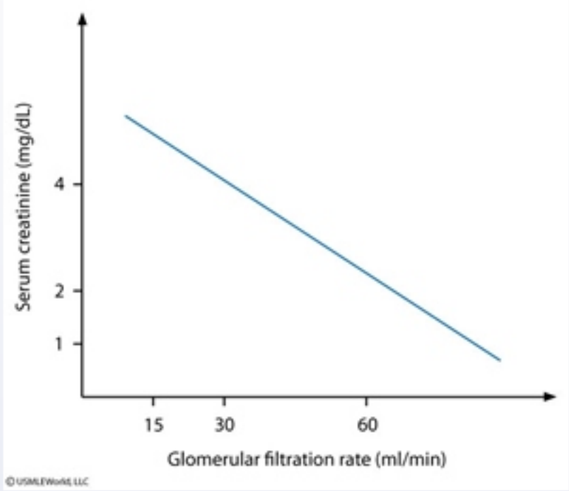


B.

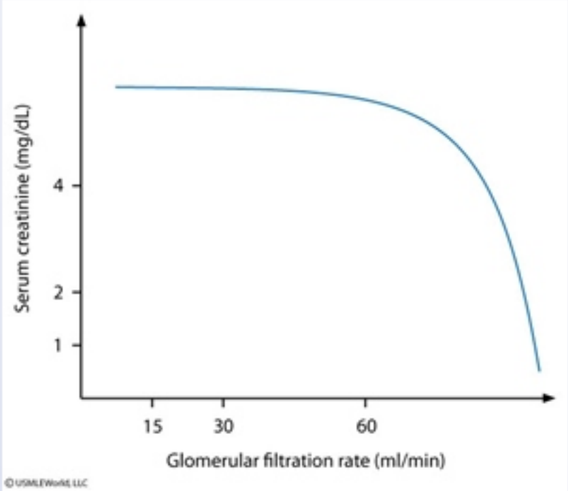


Glomerular filtration rate (ml/min)

C.

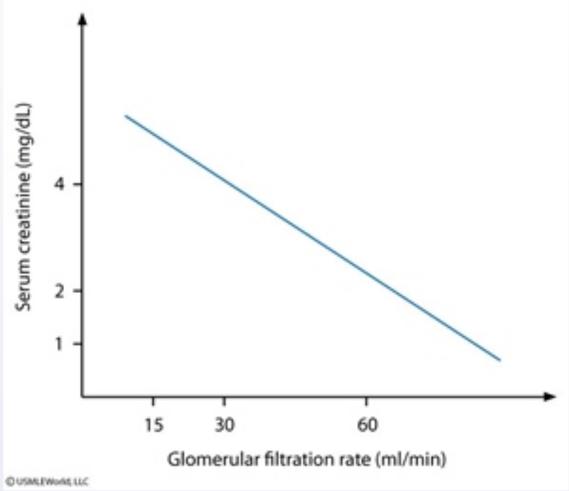


D.

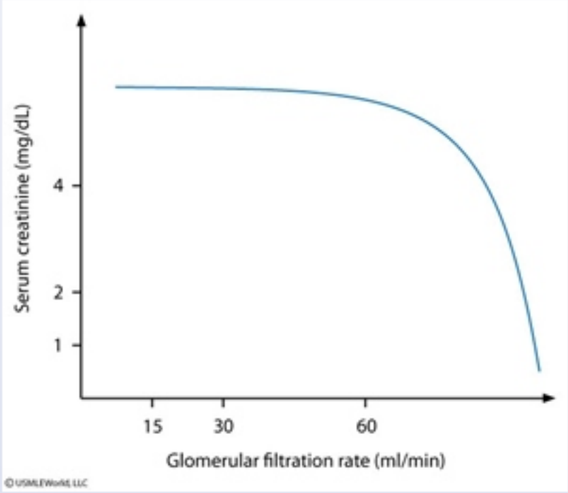


Submit

C. (22%)



D. (5%)



Omitted
Correct answer

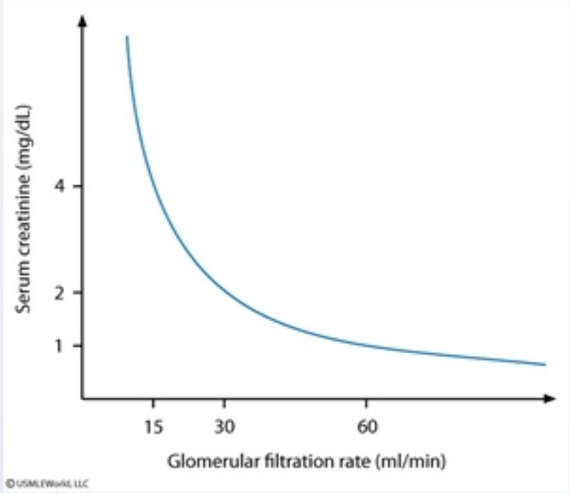
61%

05 secs

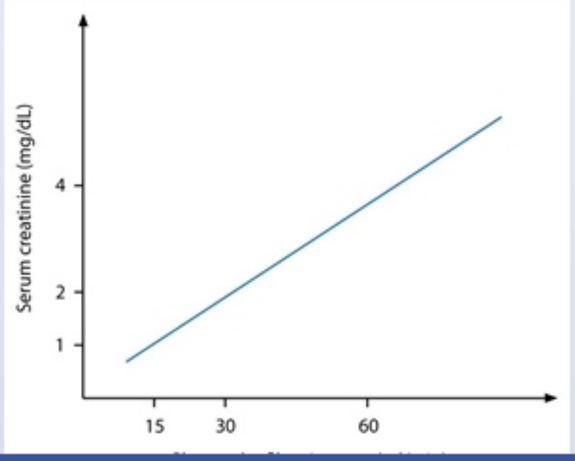
04/07/2020

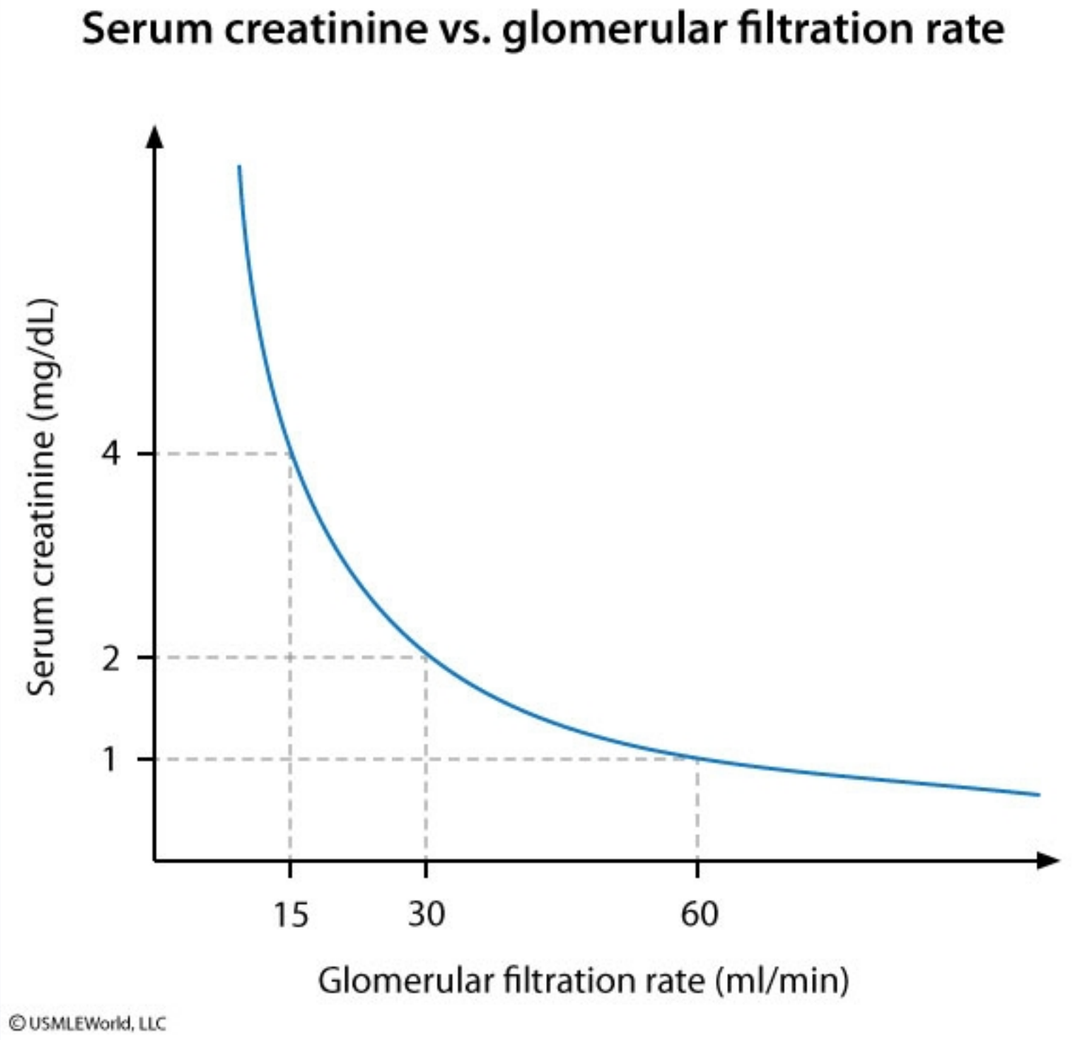
A 65-year-old man with type 2 diabetes mellitus comes to the physician for a routine follow-up appointment. He was started on oral hypoglycemic medications 12 years ago but was recently switched to long-acting insulin due to inadequate blood sugar control. His last serum creatinine level was 2.1 mg/dL. The patient is concerned about his elevated creatinine level and how it relates to his kidney function. Which of the following graphs most accurately represents the relationship between serum creatinine and glomerular filtration rate?

A. (61%)

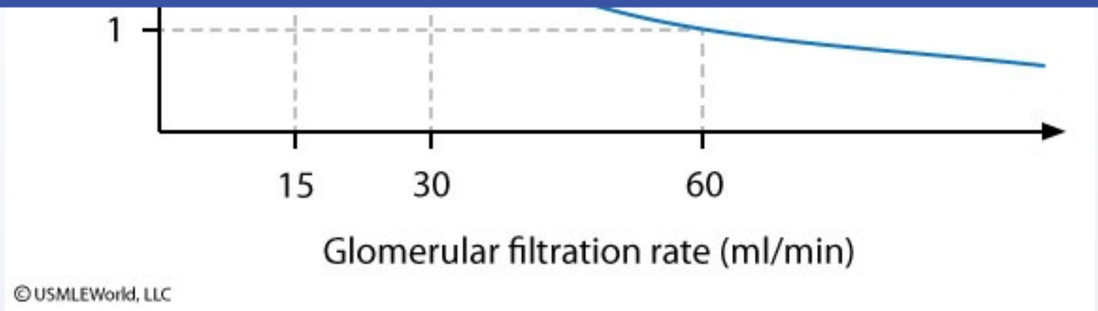


B. (9%)





Serum creatinine is the most common indicator of kidney function in clinical use. Steady-state creatinine levels are a result of the balance between creatinine synthesis in the muscle and excretion via glomerular filtration and proximal tubule secretion. For the most part, creatinine synthesis and tubular secretion remain relatively constant. As a result, serum creatinine levels depend primarily on the glomerular filtration rate



Serum creatinine is the most common indicator of kidney function in clinical use. Steady-state creatinine levels are a result of the balance between creatinine synthesis in the muscle and excretion via glomerular filtration and proximal tubule secretion. For the most part, creatinine synthesis and tubular secretion remain relatively constant. As a result, serum creatinine levels depend primarily on the glomerular filtration rate (GFR).

The relationship between serum creatinine and GFR is nonlinear. A person's serum creatinine can be essentially normal even after a 50% loss of kidney function (ie, following kidney donation or unilateral nephrectomy). Serum creatinine levels begin to rise significantly as the GFR declines to <60 mL/min (assuming no change in muscle mass). As the GFR continues to decline, the slope of the creatinine-GFR curve steepens. Consequently, when the GFR is significantly decreased, small decrements in GFR produce relatively large changes in serum creatinine. However, when the GFR is normal, relatively large decreases in GFR result in only small increases in serum creatinine. Serum creatinine is therefore an insensitive indicator for decreasing GFR when creatinine levels are normal.

Educational objective:
When the glomerular filtration rate (GFR) is normal, relatively large decreases in GFR result in only small increases in serum creatinine. Conversely, when the GFR is significantly decreased, small decrements in GFR produce relatively large changes in serum creatinine. A good rule of thumb is that every time GFR halves, serum creatinine doubles.

Physiology	Renal, Urinary Systems & Electrolytes	Chronic kidney disease
Subject	System	Topic

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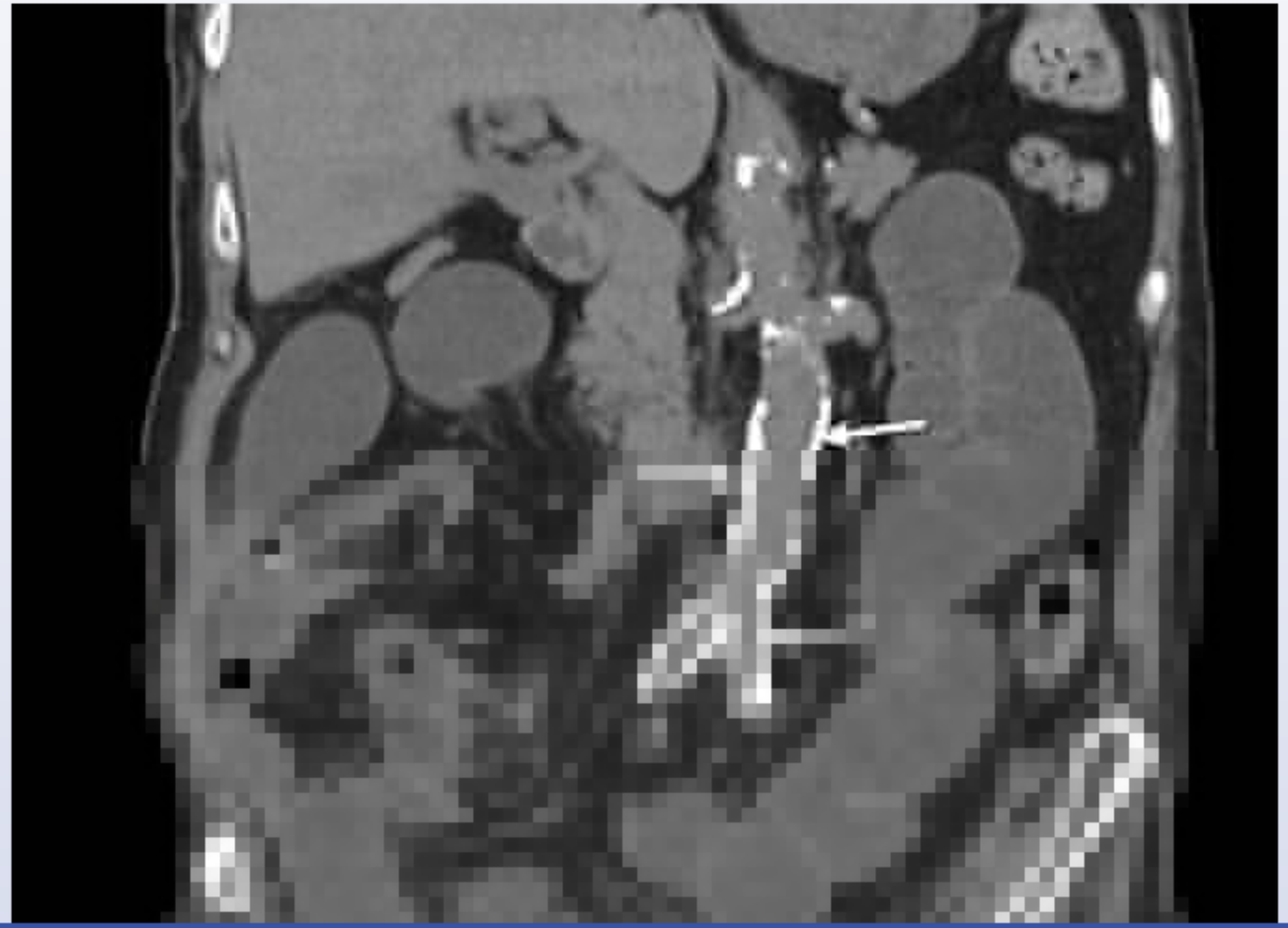
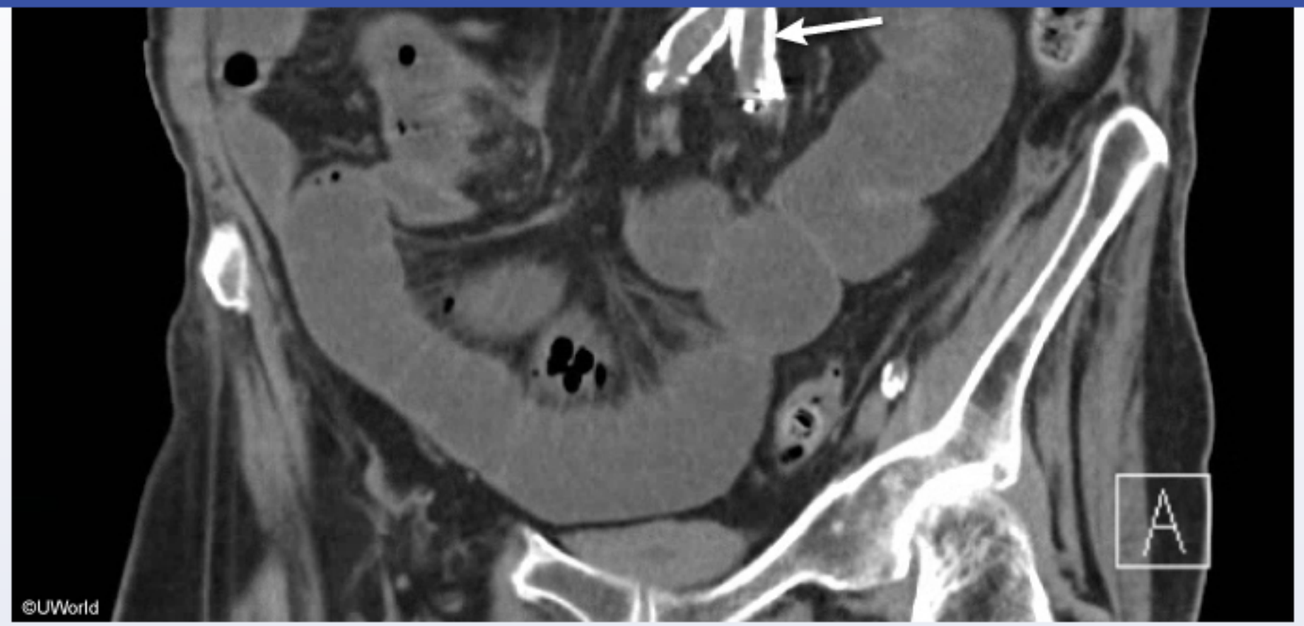
A 67-year-old woman is hospitalized due to worsening abdominal pain. The patient has long-standing end-stage renal disease from diabetic nephropathy for which she undergoes hemodialysis 3 times a week. Temperature is 37 C (98.6 F), blood pressure is 159/79 mm Hg, pulse is 97/min, and respirations are 16/min. Abdominal examination shows high-pitched bowel sounds and mild distension without rebound tenderness. Laboratory results show elevated blood urea nitrogen and creatinine. Noncontrast CT scan of the abdomen shows a small bowel obstruction. The patient also has the findings demonstrated by the arrows in the abdominal CT scan below:

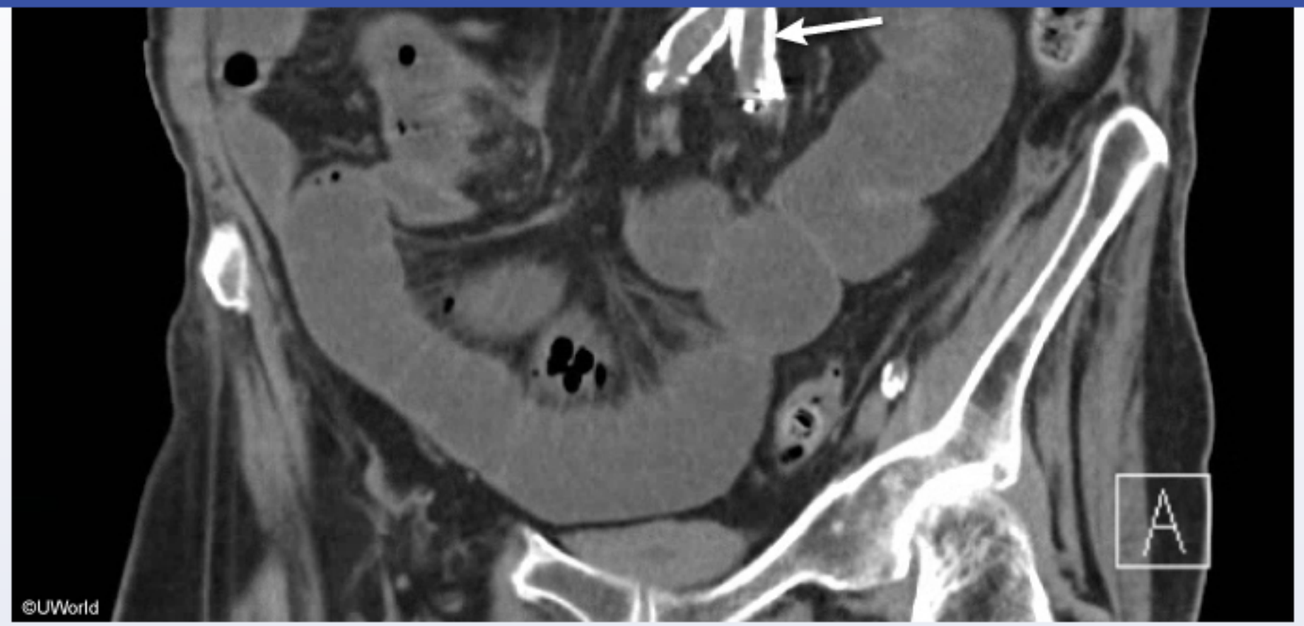




Which of the following most likely contributed to the observed findings?

- A. Hypermagnesemia
- B. Hyperphosphatemia
- C. Hypocalcemia
- D. Hypophosphatemia
- E. Recurrent hypoglycemia

Submit



Which of the following most likely contributed to the observed findings?

- A. Hypermagnesemia (4%)
- ✓ B. Hyperphosphatemia (67%)
- C. Hypocalcemia (6%)
- D. Hypophosphatemia (20%)
- E. Recurrent hypoglycemia (1%)

Omitted
Correct answer

67%
Answered correctly

05 secs
Time Spent

04/15/2020
Last Updated

This patient with end-stage renal disease (due to diabetic nephropathy) and worsening abdominal pain (due to small bowel obstruction) has extensive **vascular calcifications** (VCs) noted on abdominal CT scan. Under normal conditions, calcification inhibitors expressed by smooth muscle cells prevent the formation of calcifications. VCs occur when metabolic insults (eg, electrolyte abnormalities, dyslipidemia, oxidative stress, uremia) cause smooth muscle cells in the arterial media to differentiate into osteoblast-like cells (ie, **osteogenic differentiation**), resulting in active deposition of calcium salts within the vessels.

Excessive VCs occur frequently in patients with **chronic kidney disease**, especially those on **dialysis**, because they are predisposed to developing these calcifications through the following mechanisms:

- Electrolyte abnormalities: **Hyperphosphatemia** (decreased filtration and excretion of phosphorus) and/or **hypercalcemia** (typically iatrogenic due to the administration of calcium products as phosphate binders) promote calcification by stimulating osteogenic differentiation **(Choices C and D)**.
- **Chronic inflammation**: Inflammation, due to uremia and/or hyperlipidemia, suppresses the expression of calcification inhibitors in smooth muscle cells and damages vascular endothelial cells, providing a nidus for calcification. In addition, mineralization is proinflammatory and reinforces the cycle of inflammation within vessel walls.
- **Atherosclerosis**: In addition to its proinflammatory effects, lipid deposition in the vessel wall results in the formation of atherosclerotic lesions that can also become calcified and contribute to the calcific burden.

VCs are thought to contribute to increased cardiovascular risk and mortality but are often an **incidental finding**.

(Choice A) Magnesium inhibits extraosseous calcification, putting those with hypomagnesemia at increased risk for VCs. Hypermagnesemia would have a protective effect, making VCs less likely.

(Choice E) Diabetes mellitus is associated with a significantly increased risk for atherosclerosis and subsequent atherosclerotic calcification. However, hypoglycemia does not increase the risk for VCs.

Educational objective:
Vascular calcifications occur more commonly in patients with chronic kidney disease due to electrolyte abnormalities (eg, hyperphosphatemia, hypercalcemia) and chronic inflammation (secondary to atherosclerosis and/or uremia). These changes promote calcification and suppress calcification inhibitors, which can result in extensive vascular calcifications.

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Vascular calcifications occur more commonly in patients with chronic kidney disease due to electrolyte abnormalities (eg, hyperphosphatemia, hypercalcemia) and chronic inflammation (secondary to atherosclerosis and/or uremia). These changes promote calcification and suppress calcification inhibitors, which can result in extensive vascular calcifications.

References

- Vascular calcification: from pathophysiology to biomarkers.

Physiology	Renal, Urinary Systems & Electrolytes	Chronic kidney disease
Subject	System	Topic

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